FORMULATION, OPTIMIZATION AND EVALUATION OF CLARITHROMYCIN IMMEDIATE RELEASE FILM COATED TABLET

A dissertation submitted to

THE TAMILNADU Dr.M.G.R MEDICAL UNIVERSITY

CHENNAI- 600 032.

In partial fulfillment of the requirements for the award of Degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted
By
V.VAISHNAVI
Reg.No: 261311158

DEPARTMENT OF PHARMACEUTICS

EDAYATHANGUDY.G.S PILLAY COLLEGE OF PHARMACY

NAGAPATTINAM-611002

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Prof., Dr.M.MURUGAN, M.Pharm.,Ph.D.,

Director cum Professor,

Edayathangudy.G.S.Pillay College of Pharmacy,

Nagapattinam – 611 002.

CERTIFICATE

This is to certify that the dissertation entitled**"FORMULATION, OPTIMIZATION AND EVALUATION OF CLARITHROMYCIN IMMEDIATE RELEASE FILM COATED TABLET"** submitted by V.VAISHNAVI (Reg. No: **261311158**) in partial fulfillment for the award of degree of Master of Pharmacy to the Tamilnadu Dr. M.G.R Medical University, Chennai is an independent bonafide work of the candidate carried out under my guidance in the Department of Pharmaceutics, Edayathangudy.G.S Pillay College of Pharmacy during the academic year 2013-2015.

Place: Nagapattinam **Prof.Dr. M.MURUGAN,M.Pharm.,Ph.D.,**

Date:

Prof, Dr. D. BABU ANANTH,M.Pharm.,Ph.D.

Principal,

Edayathangudy.G.S.Pillay College of Pharmacy,

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Place: Nagapattinam **Prof.Dr.D.Babu Ananth,M.Pharm.,Ph.D.,**

Date:

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ABBREVATION

USP	**United state of pharmacopeia**
IR	**Immediate Release**
Ml	**Millilitre**
Mg	**Milligram**
G	**Gram**
µm	**Micrometer**
µg	**Microgram**
MCC	**Microcrystalline Cellulose**
Rpm	**Rotations Per Minute**
API	**Active Pharmaceutical Ingredients**
BD	**Bulk Density**
TD	**Tapped Density**
CI	**Compressibility Index**
DT	**Disintegration Time**
HR	**Hausner's Ratio**
^{o}C	**Degree Celsius**
CCS	**Croscarmellose Sodium**
AUC	**Area Under Curve**
DT	**Disintegration Time**
C_{max}	**Maximum plasma concentration**
RS	**Related Substances**

V_d	**Volume of Distribution**
$t_{1/2}$	**Half Life**
MIC	**Minimum Inhibitory Concentration**

1.INTRODUCTION

A drug is, in the broadest of terms a chemical substance that has known biological effect on humans or other animals. In pharmacology, a drug is a chemical substance used in the treatment, cure, prevention, or diagnosis of disease or used to otherwise enhance physical or mental well being . Pharmaceutical drugs may be used for a limited duration, or on a regular basis for chronic disorders.

Pharmaceutical industry, the discovery, development and manufacture of drugs and medications by public and private organizations. The modernera of the pharmaceutical industry of isolation and purification of compounds, chemical synthesis and computer- aided drug design is considered to have begun in the 19^{th} century thousands of years after intuition and trial and error led humans to believe that plants, animals, and minerals contained medicinal properties. The unification of research in the 20^{th} century in fields such as chemistry and physiology increased the understanding of basic drug discovery processes. Identifying new drug targets, attaining regulatory approval from governments agencies and refining techniques in drug discovery and development are among the challenges that face the pharmaceutical evoluation and advancement of the control and elimination of disease around the world.

In the preparation of dosages, many pharmaceuticals are ground to varying degrees of fineness. Many medicinal substances are added to water , alcohol, or another solvent so that they can be used in solution form. These may include spirits, elixers and tinctures. Ointments are one of many semisolid preparations, which also include creams, pastes and jellies. Solid pharmaceuticals include pills, tablets, lozenges and suppositories. In this form the compounds are more stables, with less risk of chemical reaction, and the dosage is easier to determine. Storage and packaging also is made simpler, and solid forms are more efficient produce.

ADMINISTERING DRUGS:

Drugs, both medicinal and recreational can be administered in a number of ways or routes. Many drugs can be administered via more than one route.

Bolus is the administration of a medication, drug or other compound that is given to raise its concentration in blood to an effective level. The administration can be given intravenously, by intramuscular, intrathecal or subcutaneous injection.

*Inhaled,(breathed into the lungs) as an aerosol or dry powder.

*Injected as a solution, suspension or emulsion either : Intramuscular, intravenous, intraperitoneal, intraosseous.

*Insufflation or snorted into the nose.

*Orally as a liquid or solid, that is absorbed through the intestines.

*Rectally as a suppository, that is absorbed to the rectum or colon.

*Sublingually, diffusing into the blood through tissues under the tongue.

*Topically, usually as a cream or ointment. A drug administered in this manner may be given to act locally or systematically.

*Vaginally as a suppository, primarily to treat vaginal infections.

Any drug delivery system is based on the nature of disease and its causing agent as well as the anatomy andphysiology of affected organ.

RESPIRATORY PROBLEMS:

In humans the anatomical features of the respiratory system include airways, lungs and the respiratory muscles. Molecules of oxygen and carbon-di-oxide are passively exchanged, by diffusion, between the gaseous external environment and the blood. This exchange process occur in the alveolar region of the lungs. The respiratory system can be subdivided into an upper respiratory tract and a lower respiratory tract based on the anatomical features. The upper respiratory tract includes the nasal passages, pharynx and larynx, while the lower respiratory tract is comprised of the trachea, the primary bronchi and lungs.

DISORDER OF THE RESPIRATORY SYSTEM CAN BE CLASSIFIED INTO FOUR GENERAL AREAS:

1) OBSTRUCTIVE CONDITIONS: Emphysema, bronchitis, asthma attacks.
2) RESTRICTIVE CONDITIONS : Fibrosis, sarcoidosis, alveolar damage, pleural effusion.

3) VASCULAR DISEASE: Pulmonary edema, pulmonary embolism, pulmonary hypertension.

4) INFECTIOUS, ENVIRONMENTAL AND OTHER DISEASES: Pneumonia, tuberculosis, asbestosis, particulate pollutants.

COMMON RESPIRATORY DISORDERS INCLUDE:

*CHRONIC OBSTRUCTIVE PULMONARY DISEASE(COPD): Irritation of the lungs can lead to asthma, emphysema and chronic bronchitis and people can develop two or three of these together.

1) CHRONIC BRONCHITIS; Any irritant reaching the bronchi and bronchioles will stimulate an increased secreation of mucus. In chronic bronchitis the air passages become clogged with mucus and this leads to a peristant cough.

2) ACUTE BRONCHITIS: It is a shorter illness that commonly follows a cold or irral infection such as the flu. It I consists of a cough with mucus, chest dis comfort or soreness, fever and sometimes shortness of breath. Acute bronchitis usually lasts a few days on weeks.

SYMPTOMS FOR BOTH ACUTE AND CHRONIC BRONCHITIS:

i)Peristant cough may produce mucus. ii)Wheezing iii)Low fever and chills

iv)Chest tightening v)Sore throat vi)Body ache vii) Breathlessness

viii)Headache ix)Blocked nose and sinuses.

EMPHYSEMA: The delicate walls of the alveoli break down, reducing the gas exchange area of the lungs. The condition develops slowly and is seldom a direct cause of death.

ASTHMA: Periodic constriction of the bronchi and bronchioles makes it more difficult to breathe.

PNEUMONIA: Any infection of the alveoli. It can be caused by many kinds of both bacteria viruses. Tissue fluids accumulate in the alveoli reducing the surface

area exposed to air. If enough alveoli are affected, the patient may need supplemental oxygen.

ROLE OF CLARITHROMYCIN:

Immediate release drug delivery system are based on single or multiple unit reservoir or matrix system, which are designed to provide of time. Immediate release drug delivery is desirable for drugs having long biological half life, high bioavailability. Oral drug delivery is the most desirable and preferred method administering therapeutics agent for their systematic effect. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of new entities and pharmaceutical formulation, mainly because of patient acceptance, convenience in administration and cost effective manufacturing process.

Clarithromycin is a macrolide antibiotic with broad spectrum of activity. It is given the treatment of respiratory tract infection in the skin and soft tissue infection. Clarithromycin may be given to eradicate H.pylori in treatment regimen's for peptic ulcer diseases. Clarithromycin has invitro antibacterial activity against typical (streptococcus, pneumonia, haemophilus, influenza, Moraxella catarhalis) atypical (mycoplasma pneumonia, chlamydia pneumonia, legionella pneumophilla) pathogens commonly associated acquired lower respiratory tract infections.

Clarithromycin is rapidly absorbed from the GIT and undergoes first pass metabolism. The bioavailability of the drug is about 55% . The terminal half life of clarithromycin is reportedly about 3-4 hrs. Compared with erythromycin, clarithromycin possesses greater acid stability, improved pharmacokinetic properties and fewer GIT, rapid gastrointestinal absorption, highly soluble at acidic pH absorption of clarithromycin is unaffected by food. More than half of an oral dose is systematically available as the parent drug and the active 14- hydroxyl metabolite, pharmacokinetics are non linear, with plasma concentration increasing in more than proportion to the dosage. First pass metabolism results in the rapid appearance of the active metabolite. 14-Hydroxy clarithromycin and its active metabolite are found in greater concentrations in the tissue and fluids of the respirator, it has higher eradication rate invivo to H.pylori. The recommended dosage regimen for these types of infection in adult patients is

250mg to 500mg twice daily for 7-14 days of the immediate- release oral formulation of clarithromycin.

MEDICATIONS 6

Therapy addressing specific symptoms is the mainstay for most URIs. Most URIs are self-limited viral infections, which can be resolved without prescription of drugs. Recognizing viral and bacterial diseases for which specific therapy is available is important. Antibacterial therapy is useful for patients with group A streptococcal pharyngitis, bacterial sinusitis, epiglottis's, pertussis, or diphtheria. Patients with HSVinfection or gonococcal upper airway disease also benefit from specific treatment. In immune compromised patients, infections may be appropriate, especially if lower airway disease is suspected. In general, antiviral do not provide clinical benefits in persons with viral pharyngitis. However, in patients who are immune compromised, antiviral have a role in treating illness that might progress. Acyclovir, famciclovir, and valacyclovir are recommended for patients with severe HSV pharyngitis and for immune compromised patients. Ganciclovir or foscarnet are recommended for the treatment of cytomegalovirus infections in immune compromised patients.

1.2. CHEMOTHERAPY7,8,9,10

Chemotherapy can be defined as the use of chemical in infectious diseases to destroy the microorganisms without damaging the host tissues.

1.2.1. ANTIBIOTICS:

Antibiotics are substances produced by a microorganism that suppresses the growth of or destroy other microorganisms.

1.2.2. CLASSIFICATION:

Antibiotics are classified in many ways based on chemical structure, its spectrum of activity, pharmacological activity.

1.Basedonchemicalstructure7

ANTIBIOTICS

1.SULPHONAMIDES : Sulphamethaoxazole, Sulphadiazine,

Sulphamethaoxazole+Trimethaprim.

2.QUINOLONES : Nalidixic acid, Ciproflaxacin, oflaxacin, Levoflaxacin

3.B-LACTUM : Penicillin, ampicillin, amoxicillin, cephalosporins

4.TETRACYCLINES : Doxycyclines

5.MACROLIDES : Erythromycin, Azithromycin, Clarithromycin, Telithromycin

6.AMINOGLYCOCIDES : Streptomycin, Neomycin, Gentamycin, kanamycin.s

2. Based on mechanism of action

1. Inhibit cell wall synthesis

- Penicillins, cephalosporins, carbapenems, monobactam, vancomycin, bacitracin, cycloserine.

2. Damage cell membranes(cause leakage of cell membranes)

- Polymyxins, amphotericin B, nystatin.

3. Bind to ribosomes and inhibit protein synthesis:

- Chloramphenicol, tetracyclines, erythromycin, amino glycosides, clindamycin.

4. Inhibit DNA gyrase

- Flouroquinolones

5. Inhibit DNA function

- Rifampicin

6. Interfere with metabolic steps

- Sulphonamides, sulphones, trimethoprim, pyrimethamine.

Antimicrobials may also be classified as extent of action:

1. Bacteriostatic:

These are the agents that suppress the growth of bacteria.

Eg: Sulphonamides, Tetracyclines, Linezolid, Chloramphenicol, Clindamycin.

2. Bactericidal:

These are the agents that kill the bacteria.

E.g: Penicillins, Cephalosporins, Amino glycosides, Flouroquinolones, Rifampicin, Metronidazole.

However, some drugs may be bacteriostatic at low doses and bactericidal at higher doses. E.g: Erythromycin may be bacteriostatic to some microorganisms and bactericidal to others. Eg: Chloramphenicol is bactericidal to H.influenzae, S.pneumoniae and N.menigitidis, while it is bacteriostatic to other microorganisms.

1.2.3. ANTIBACTERIAL SPECTRUM:

An antimicrobial may have a narrow or broad spectrum of activity.

- Narrow spectrum antibiotics:

E.g: penicillin G – gram positive organisms

Amino glycosides –gram negative organisms.

- Broad spectrum antibiotics:

E.g: Tetracyclines and Chloramphenicol: gram positive and gram negative organisms, ricketssiae, chlamydiae, mycoplasma.

Broad spectrum antibiotics are so called because in addition to suppression of gram positive and gram negative bacteria, they also inhibit the growth of other microorganisms like ricketssiae, chlamydiae, mycoplasma and some protozoa. But in practice the term ‘broad spectrum’ is often used to include all antimicrobials with a wide spectrum of activity i.e., those effective against both gram positive and gram negative organisms.

E.g: Ampicilin.

1.2.4. MACROLIDES7,8 ,9,10,11

Macrolide are group of antibiotics produced by various strains of streptomyces. They have three common chemical characteristics like a large non-planar strain less ring, a keto group, a glycosidically linked amino sugar.Usually the lactone ring has 12, 14 or 16 atoms in it, unsaturated with an olefinic group conjugated with the ketone function. They may have a neutral sugar also, in addition to the amino sugar, which is linked glycosidically to the lactone ring.

The macrolides are a group of antibiotics with a structure to which one or more deoxy sugars are attached. Erythromycin was the first of these drugs to find clinical application, both as a drug of first choice and as an alternative to penicillin in individuals who are allergic to lactam antibiotics. The newer members of this family, clarithromycin (a methylated form of erythromycin) and azithromycin (having a larger lactone ring), have some features in common with, and others that improve on, erythromycin. Telithromycin, a semi synthetic derivative of erythromycin, is the first ketolide• antimicrobial agent that has been approved and is now in clinical use.

Ketolides and macrolides have very similar antimicrobial coverage. However, the ketolides are active against many macrolide-resistant gram-positive strains.

MECHANISM OF ACTION:

Macrolides are protein synthesis inhibitors. The mechanism of action of macrolides is inhibition of bacterial protein biosynthesis, The drugs act by binding to cell membranes and causing changes in protein function and they are thought to do this by preventing peptidyltransferase from adding the peptidyl attached to t-RNA to the next amino acid as well as inhibiting ribosomal translocation. Another potential mechanism is premature dissociation of the peptidyl-tRNA from the ribosome.

Macrolide antibiotics do so by binding reversibly to the P site on the subunit 50S of the bacterial ribosome. Macrolides inhibit the translocation of the growing peptide chain from A site to P site. Hence A site is not available for binding of next aminoacid (brought by t-RNA). This action is mainly bacteriostatic, but can also be bactericidal in high concentrations. Macrolides tend

to accumulate within leukocytes, and are, therefore, transported into the site of infection.

ERYTHROMYCIN:

It is a fermentation product of the fungus streptomyces erythreus. Its antibacterial spectrum resembles that penicillin. It is mainly effective against gram positive cocci including the streptococci, staphylococci and pneumococci, Neisseria, some strains of H. influenza, C.diphtheriae, Mycoplasma pneumonia, Rickettsiae and Treponemas are also inhibited by low concentration. The drug is effective against penicillin resistant staphylococci can develop resistance to erythromycin. Its activity increases with an increase of pH upto 8.

ROXITHROMYCIN:

It is a newer macrolide (azalides) have a similar spectrum of activity as erythromycin. They are acid stable, longer acting, more potent, better absorbed and has a better tissue penetrability compared to erythromycin. It is rapidly absorbed from the gut with a bioavailability of 50%, food interferes with its absorption. Most of the drug is excreted either through feces, unchanged or as metabolites. The adverse effects are similar to that of erythromycin. It should be taken before 30 min of food. It is used in ear, throat, respiratory tract and non-gonococcal genitourinary infections. It is more expensive.

AZITHROMYCIN:

This azilide antibiotic differs chemically from the macrolide group in that the lactone ring contains a nitrogen atom. It has similar activity as erythromycin but in addition, it act against gram-positive bacilli including H.influenzae. It also act against Mycobacterium avium complex (MAC). It is most active at pH 7.4 and above. It has better tissue penetrability, longer half-life than erythromycin. It can be used in respiratory tract infections, cervicitis and urethritis.

KETOLIDES

Ketolides are modified macrolides that are similar to newer macrolides and also related to erythromycin with similar antibacterial spectrum. The main example of this category is Telithromycin. It is resistant to pneumococci. The drug is potent inhibitor of CYP3A4.

1.4. INTRODUCTION FOR TABLETS:

The oral route of drug administration is the most important method of administrating drugs for systemic effects. Oral drug delivery has been known for decades as the most widely utilized route of administered among all the routes that have been employed for the systemic delivery of drug via various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration belief that by oral administration of the drug is well absorbed.

All the pharmaceutical products formulated for systemic delivery via the oral route of administration irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage forms (either solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology, pharmacokinetics, pharmacodynamics and formulation design is essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form.

1.4.1. TABLETS13,15,16,17,18,19.20,21,22.23.24.25.26

Tablets are solid dosage forms containing medicinal substances with or without suitable diluents. They are the most widely preferred form of medication both by pharmaceutical manufacturer as well as physicians and patients. They offer safe and convenient ways of active pharmaceutical ingredients (API) administration with excellent physiochemical stability in comparison to some other dosage forms, and provide accurate dosing.

They can be mass-produced with robust quality controls and other different branding possibilities by means of colored film coating different sizes and shapes. Tablets are usually solid, right circular cylinders, the end surfaces of which are flat or convex and the edges of which may be bevelled.

1.4.2. PROPERTIES OF TABLETS

The attributes of an acceptable tablet are as follows:

- The tablet must be sufficiently strong and resistance to shock and abrasion and to withstand handling during manufacturing, packaging, shipping and use. Hardness and friability tests measure this property.

- Tablet must be uniform in weight and in drug content of the individual tablet.
- This is measured by the weight variation and content uniformity tests.
- The drug content of the tablet must be bioavailable. This property is measured by the dissolution test. Accurate bioavailability can be obtained from the drug levels of the drug after its administration
- Tablets must be elegant in appearance and must have characteristic shape, color and other markings necessary to identify the product.
- Tablets must retain all these functional attributes, which include drug stability and efficacy.

ADVANTAGES OF TABLETS 15

- They are easy to administer.
- They are a unit dosage form, and they offer the greater capabilities of all oral dosage forms for the greatest dose precision and the least content variability.
- Their cost is lowest of all oral dosage forms.
- They are the lightest and most compact of all oral dosage forms.
- Product identification is potentially the simplest and cheapest, requiring no additional processing steps when employing an embossed or monogrammed punch face.
- They are in general the easiest and cheapest to package and ship of all oral dosage forms.
- They may provide the greatest ease of swallowing with least tendency for “hang-up” above the stomach. Especially when coated, provided that tablet disintegration is not excessively rapid.
- They tend themselves to certain special release profile products, such as enteric or delayed release products.
- They are better suited to large-scale production than other unit oral forms.

They have the best-combined properties of chemical, mechanical and microbiological stability of all the oral forms.

- One of the major advantages of tablet over capsules is that the tablet is essentially “tamperproof dosage form.”

2. DISADVANTAGE OF TABLETS 15

- Some drugs resist compression into dense compacts, owing to their amorphous nature or flocculent, low-density character.

- Drugs with poor wetting, slow dissolution properties, intermediate to large dosages, optimum absorption high in the gastrointestinal tract, or any combination of these features may be difficult or impossible to formulate and manufacture as a tablet that will still provide adequate or full drug bioavailability.

- Bitter tasting drugs, drugs with objectionable odor or drugs that are sensitive to oxygen or atmospheric moisture may require encapsulation or a special type of coating which may increase the weight of the finished products.

- A major disadvantage of capsules over tablets is their higher cost.

TYPES OF TABLET 16,17

The main reasons behind formulation of different types of tablets are to create a delivery system that is relatively simple, inexpensive to manufacturer, dosage form that is convenient from patient’s perspective and utilize an approach that is un-likely to add complexity during regulatory approval process. To understand each dosage form, tablets here are classified by their route of administration, by the type of drug delivery system and by the formulation characterized.

ORAL TABLETS FOR INGESTION

These tablets are meant to be swallowed intact along with a sufficient quantity of water. Exception is chewable tablet. Over 90% of the tablets manufactured today are ingested orally. This shows that this class of formulation is the most popular worldwide and the major attention of the researcher is towards this direction.

These include:

1. Standard compressed tablets
2. Multiple compressed tablets

- Compression coated tablet
- Layered tablet
- Inlay tablet

3. Modified Release tablet
4. Delayed action tablet
5. Targeted tablet

- Floating tablet
- Colon targeting tablet

6. Chewable tablet
7. Dispersible tablet

Tablets used in the oral cavity

The tablets under this group release API in oral cavity or to provide local action in this region. The tablets under this category avoids first-pass metabolism, decomposition in gastric environment, nauseatic sensations and gives rapid onset of action. The tablets formulated for this region are designed to fit in proper region of oral cavity. These include:

- Lozenges and troches
- Sublingual tablet
- Buccal tablet
- Dental cones
- Mouth dissolved tablet

Tablets administered by other routes

The tablets administered by other route, which avoid from passing through gastro intestinal tract. These tablets may be inserted into other body cavities or directly placed below the skin to be absorbed into systemic circulation from the site of application. These include:

- Vaginal tablet
- Implants

Formulation characteristics

Tablets are also classified according to their formulation characteristics such as

- Immediate release tablets
- Effervescent tablets
- Melt in mouth or fast dissolving tablets
- Delayed release or extended release tablets

1.4.9.MANUFACTURING DEFECTS IN TABLETS18

Processing problems are categorized into following are:

1. Defects during tablet processing :

- Capping
- Lamination
- Cracking
- Picking
- Sticking/filming
- Binding
- Chipping

2. Defects due to other factors :

- Mottling

3. Defects due to machine :

- Poor flow pattern
- Double impression

1.4.10. TABLET COATING15,19,20

Coated tablets are defined as “tablets covered with one or more layers of mixture of various substances such as natural or synthetic resins, gums, inactive and insoluble filler, sugar, plasticizer, polyhydric alcohol, waxes, authorized coloring material and sometimes flavoring material .

Coating may also contain active ingredient. Substances used for coating are usually applied as solution or suspension under conditions where vehicle evaporates.

A) ASPECTS OF TABLET COATING

I. THERAPY

i) Avoid irritation of oesophagus and stomach

ii) Masks bitterness

iii) Avoid inactivation of drug in the stomach

iv) Improve drug effectiveness

v) Prolong dosing interval

vii) Improve patient compliance

II. TECHNOLOGY

i) Reduce influence of moisture

ii) Avoid dust formation

iii) Reduce influence of atmosphere

iv) Improve drug stability

v) Prolong shelf life

III. FORMULATION

i) Withstand mechanical process

ii) Maximum adhesion of the coating to the tablet surface, especially when a logo is present

iii) A smooth film coat with uniform thickness

IV. MARKETING

i) Improve product identity

ii)Improve appearance and acceptability

B) BASIC PRINCIPLE OF TABLET COATING 19,20

The principle of tablet coating is relatively simple. Tablet coating is the application of coating composition to moving bed of tablets with concurrent use of heated air to facilitate evaporation of solvent.

C) TYPES OF TABLET COATING PROCESS

1.SUGAR COATING

Compressed tablets may be coated with colored or uncolored sugar layer. The coating is water soluble and quickly dissolves after swallowing. Sugarcoat protects the enclosed drug from the environment and provides a barrier to objectionable taste or order. The sugar coat also enhances the appearance of the compressed tablet and permit imprinting manufacturer's information. Sugar coating provides a combination of insulation, taste masking, smoothing the tablet core, coloring and modified.

The disadvantages of sugar coating are time, expertise required in the coating process, increase in size, weight and shipping costs.

Sugar coating process involves five separate operations:

I. SEALING/WATER PROOFING: Provides a moisture barrier and harden the tablet surface.

II. SUB COATING: Causes a rapid buildup to round off the tablet edges.

III. GROSSING/SMOOTHING: Smoothes out the sub coated surface and increases the tablet size to predetermine dimension.

IV. COLORING: Gives the tablet its color and finished size.

V. POLISHING: Produces the characteristics gloss.

2. FILM COATING

Film coating is more favored over sugar coating. Now days, sugar coating is replaced with film coating, because the sugar coating process was a skilled manipulative process and could last for even five days. The operator must be highly skilled for such coating. Hence film coating is preferred over sugar coating.19

a.BASIC PRINCIPLES INVOLVED IN FILM COATING

1. Insulation which influences the release pattern as little as possible and does not markedly change the appearance.

2. Modified release with specific requirement and release mechanism adapted to body function in the digestive tract.

3. Color coating which provides insulation or is combined with modified release coating.

b. MATERIALS USED IN FILM COATING

I. Film formers, which may be enteric or non-enteric

II. Solvents

III. Plasticizers

IV. Colorants

V. Opaquant-Extenders

VI. Miscellaneous coating solution components

c. FILM DEFECTS

Include sticking and picking, roughness, orange-peel effect, bridging and filling, blistering, hazing/dull film, color variation, cracking.

3. ENTERIC COATING

Enteric coated tablets are tablets with a coating that resist dissolution or disruption in the stomach but not in the intestine, thereby allowing for tablet transit through the stomach in favor of tablet disintegration and dissolution and absorption from the intestine.

The materials used in enteric coating are shellac, hydroxy propyl methyl cellulose phthalate, poly vinyl phthalate and cellulose acetate phthalate.

4. SPECIALIZED COATING : It includes Compression coating, Electrostatic coating, Dip coating, Vacuum film coating.20

1.4.11. EVALUATIONOFTABLET

Tablets when formulated may undergo physical and chemical changes, which may alter their bioavailability. Therefore, the tablets are to be evaluated before dispensing to ensure their stability and bioavailability throughout their shelf life. Evaluation of tablets can be carried out by the following test.

A. CHARACTERISTICS OF GRANULES

- Flow Ability
- Compressibility
- Bulk density
- Tapped density

B. COMPRESSED TABLET CHARACTERISTICS

UNOFFICIAL TESTS

- Tablet appearance
- Organoleptic parameters

- Identification markings on the tablets
- Size and shape of the tablet
- Thickness of the tablet
- Hardness of the tablet
- Friability of the tablet

OFFICIAL TESTS (According to IP)

- Weight variation test
- Content uniformity
- Disintegration test
- Dissolution test

1.5. STABILITY STUDIES AS PER ICH GUIDELINES

Stability is defined as the capacity of a drug substance or drug product to remain within the established specifications to maintain its identity, strength, quality and purity throughout the retest or expiration dating period.

The objective of stability study is to determine the shelf life, namely the time period of storage at a specified condition within which the drug product still meets its established specifications.

Stability is an essential factor of quality, safety and efficacy of a drug product. A drug product, which is not of sufficient stability, can result in changes in physical (like hardness, dissolution rate, phase separation etc) as well as chemical characteristics (formation of high risk decomposition substance.The chemical stability of drug is of great importance since it becomes less effective as it undergoes degradation. Also drug decomposition may yield toxic by products that are harmful to the patient. Microbiological instability of a sterile drug product could also be hazard.

II.AIM AND OBJECTIVE OF WORK

The present study aims at developing a clarithromycin immediate release tablet formulation for the effective treatment of respiratory tract infections.

Clarithromycin is macrolide antibiotic produced by various strains of streptomyces. The mechanism of action of clarithromycin is inhibition of bacterial protein biosynthesis. Clarithromycin is acid stable and it is rapidly absorbed from the gastrointestinal tract after oral administration. The plasma half-life of clarithromycin is 2-3 hours. The usual duration of treatment of clarithromycin is 6 to 14 days. Clarithromycin is economically beneficial than all other macrolide antibiotics.

- The main objective of this study was to

i) To formulate clarithromycin immediate release film coated tablet.

ii) To evaluate the formulated tablets as per requirements of standards.

iii) To optimize the trial batch by 3^2 full factorial design study.

iv) To evaluate the optimized batches.

v) To determine the best batch by dissolution studies.

vi) Drug release profile was compared with innovator product.

vii) To calculate the similarity and dissimilarity factor for both drug release profile and innovator drug product.

viii) To perform stability studies for the optimized batch for 3 months at $40^{o}C/75\%$ RH.

PLAN OF WORK

A) Literature review

B) Drug profile

C) Excipient profile

D) Innovator product specification

E) Preformulation studies

a) Evaluation of API

- ✓ Description
- ✓ Solubility
- ✓ pH
- ✓ Melting point
- ✓ Chemical nature
- ✓ Hygroscopicity
- ✓ Particle size distribution
- ✓ Loss on drying

b) Drug excipient compatibility studies

- ✓ Physical observation
- ✓ FT-IR studies

F) Selection of excipients by finger print method

G) Formulation of uncoated clarithromycin immediate release tablets by wet granulation method.

H) Evaluation of the granules.

I) Evaluation of physical parameters for compressed tablet.

i. Weight variation

ii. Thickness

iii. Hardness

iv. Friability

v. Disintegration

vi. Determination of drug content

J) In vitro dissolution studies.

K) Coating of the formulated clarithromycin immediate release tablets.

L) Evaluation of the coated tablets.

M) Optimization of the trial batch by full factorial design.

N) Evaluation of the optimized batches.

O) Comparison of the drug release for optimized batch and innovator product.

P) Stability studies of the optimized formulation.

III. LITERATURE REVIEW

- Saleki-Gerhardt et al., US patent 1999 jul.6/5, 919, 48929 Provided a process for the aqueous granulation of a macrolide antibiotic which comprises mixing a macrolide and a carbomer, wetting the mixture with water and blending the mixture to allow formulation of a macrolide antibiotic-carbomer granule.

- Wadhwa et.al., US patent Nov.4,2003/US 6,642,276 B230 Related to an controlled release macrolide pharmaceutical formulation. It gives a information about method of preparation, isolating and characterizing soluble and stable citrate salt of macrolides and use in all solid dosage forms of macrolides.

- Margret Chandra, et al.,31 Developed a mucoadhesive tablets of clarithromycin which were designed to prolong the gastric residence time after oral administration. Clarithromycin is in a class of medications called macrolide antibiotics. It works by stopping the growth of bacteria. matrix tablets of clarithromycin were formulated using four mucoadhesive polymers namely carbopol 974P, HPMC K15M and HPMC K4M carried out studies for weight variation, thickness, hardness, content uniformity, swelling index, mucoadhesive force and in vitro drug release. Formulation of F9 and F12 which were formulated by using polymers, HPMC K14M, HPMC K15M and carbopol 974P provided controlled release of clarithromycin over the period of 12 hrs. The cumulative % of drug release of formulation F9 and F12 were 93.16 and 96.82 respectively. The stability studies showed that there was no significant change in adhesive strength, invitro release when stored at room temperature, 40oC, and 2-8oC for a period of 30 days.
- Rahul Suture. et al.,32 Developed a drug delivery systems to gastro intestinal tract for treatment of H.pylori induced peptic and duodenal ulcers, in the present study an attempt has been made to develop and evaluate hydro dynamically balanced matrix tablets of
- clarithromycin which were prepared by using hydroxypropyl methyl cellulose K 4M (HPMC K4M), hydroxypropyl methylcellulose K 15M (HPMC 15 M) and chitosan with NaHCO3 as gas forming agent. These matrix tablets were evaluated for their physiochemical properties, buoyancy and tablet density. Effect of hardness on matrix revealed that increase in hardness affects

buoyancy lag time due to reduction in porosity of compact mass. The release rate determined on 0.1N HCl (pH1.2) showed controlled release of drug following non-Fickian mechanism

- N.B. Santha Sheela. et.al.,33 Formulated a floating sustained release tablets of clarithromycin, by using a combination of hydrophilic polymers (different grades of hydroxypropyl methylcellulose), kollidon SR and an effervescent substance (sodium bicarbonate). The formulation were evaluated to study the effect of sodium bicarbonate concentration on the floating lag time, total duration of floating, invitro dissolution release profile and the effect of different fillers and ethyl cellulose concentration on the release profile of drug. It was found that among all the formulations, formulation F4 (HPMC K15M, Avicel 102 PH and sodium bicarbonate) was found to be the optimum formulation as it had good swelling property, floating time and drug releases. The drug release of optimized formulation was found to follow zero order, Higuchi and Korsemeyer-peppas kinetic models.

- Sanjay S. Patel, et.al.,34 Developed a floating matrix tablets designed to prolong the gastric residence time after oral administration, at a particular site and controlling the release of drug especially useful for achieving controlled plasma level as well as improving bioavailability. With this objective, floating dosage form containing clarithromycin as drug was designed for the treatment of Helicobactor pylori. Tablets containing hydroxy propyl methyl cellulose (HPMC), drug and different additives were compressed using wet granulation and D-optimal design technique. The study shows that tablet composition and mechanical strength have great influence on the floating properties and drug release. Incorporation of gas – generating agent together with polymer improved drug release, besides optimal floating (floating lag time <30 seconds; total floating time 10 hours). The drug release was sufficiently sustained (more than 8 hours) and anomalous diffusion as well as zero-order was confirmed. Optimization of the evaluating parameters with "design expert" software was employed to get final optimized formulation. The optimized formulation was obtained using 62.5% clarithromycin, 4.95% HPMC K15M, 18.09% HPMC k4M, 12.96% sodium bicarbonate which gave floating lag time <30 seconds with a total floating time > 10 hours, invitro release profile very near to the target in vitro release profile and follows anomalous diffusion as well as zero order pattern of release.

- Balkrushna K. Patel. et.al., 35 Described the preparation of Clarithromycin hydrophilic matrix tablets by direct compression technique followed by invitro floating characterization statistically. The floating hydrophilic matrix tablets prepared by using different grades of polymer (HPMC) of varying concentrations, different concentration of sodium bicarbonate and varying ratios of MCC. Floating properties such as FLT, TFT, and Swelling index. Tablet hardness had found to be affecting on floating behavior. Hydrophilic matrix floating tablets of clarithromycin were developed to increase the gastric residence time, which leads to increased bioavailability by giving sufficient time to release the drug in Gastro Intestinal tract.
- Shah S.H. et.al.,36 Developed a rate-controlled oral drug delivery systems to overcome physiological adversities, such as short gastric residence times (GRT) and unpredictable gastric emptying times (GET). It is known that differences in gastric physiology, such as, gastric pH, and motility exhibit both intra-as well as inter-subject variability demonstrating significant impact on gastric retention time and drug delivery behavior. This triggered the attention towards formulation of stomach specific (gastro retentive) dosage forms. This dosage forms will be very much useful to deliver 'narrow absorption window' drugs. Several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery systems (FDDS), swelling and expanding systems, polymeric bioadhesive systems, high-density systems, modified-shape systems and other delayed gastric emptying devices. In this review, current & recent developments of stomach specific FDDS are discussed.
- Aphale Sanjivini. et.al., 37 Developed hollow floating microspheres of clarithromycin for gastro retention using Eudragit polymers prepared by emulsion solvent diffusion method. Eudragit S 100, RS 100, RL 100, L 100 and L 100 55 were used to prepare hollow microspheres. A drug – excipient compatibility study was performed using FTIR. The microspheres were characterized for shape and surface morphology by scanning electron microscopy. They were evaluated for particle size, flow properties, bulk density, % drug entrapment efficiency, floating properties and in-vitro drug release. The residual solvent content was determined after varying the stirring time. Drug to polymer ratio was varied from 1: 1 to 1: 3 and its effect on particle size and drug release was studied. The microspheres exhibited round shape, porous surface, prolonged drug release and buoyancy for more than eight hours. As the drug to polymer ratio is increased. The particle size increased and the drug release rate decreased.

- P.K. Gupta. et. al., 38 Summarized the results of in vitro and invivo studies conducted to evaluate the feasibility of developing an intramuscular (i.m.) formulation of clarithromycin by encapsulating in a biodegradable polymer, poly(lactic acid) (PLA).
- Drug/PLA microspheres were prepared by solvent evaporation and recovered by filtration or spray-drying. Variations in processing parameters, e.g., polymer concentration in the dispersed phase, type of continuous phase and the recovery process, did not appreciably alter microsphere particle shape, size or drug loading. In 0.05 M phosphate buffer (pH 7.4, at 37°C), compared to the dissolution of bulk drug, the microsphere formulations demonstrated good sustained release properties. In a preliminary in vivo study, 10 mg/kg drug was administered i.m. to groups of three dogs as a suspension of bulk drug or via PLA microspheres. Blood samples were collected over time to monitor drug and creatinine phosphokinase (CPK) concentrations. Both groups demonstrated drug concentrations ≥ 1 μg/ml for about 4 days after dosing. Also, the serum CPK concentrations in both groups were low, and compared well with those observed following the i.m. administration of placebo microspheres. The animals receiving drug/PLA microspheres demonstrated minor swelling at the site of injection which lasted for 12–24 h; however, the bulk drug treatment group exhibited much greater swelling lasting for 2–3 days. Since these observations do not correlate with serum CPK levels, alternative quantitative models are required to conclusively evaluate the potentials of microsphere formulations for the i.m. delivery of painful/irritating compounds like clarithromycin.
- Chudiwal P.D. et.al., 39 Developed an optimized gastro retentive drug delivery system (GRDDS) of clarithromycin floating microspheres by the optimization technique. The clarithromycin microspheres were prepared by non aqueous solvent evaporation method using different grades of hydroxyl propyl methylcellulose (HPMC) such as HPMC 15M (15cps), HPMC K4M (4000cps), HPMC 100LV (100cps) and ethyl cellulose (EC). The prepared microspheres were characterized by polymer compatibility, percentage yield, buoyancy percentage, drug entrapment efficiency and in vitro drug release. An optimized formulation investigated for morphology and particle size analysis by scanning electron microscopy. A 32 factorial design was employed in formulating the GRDDS with different viscosity grades of HPMC (X1) and polymer-to polymer ratio Ethyl cellulose: HPMC (X2) as independent variables. Four dependent variables were percentage of yield, drug entrapment efficiency, buoyancy percentage and

percentage of cumulative drug release of microspheres after 12h (R12h). The main effect and interaction terms were quantitatively evaluated using a mathematical model. Regression analysis and numerical optimization were performed to identify the best formulation. The predicted values agreed well with the experimental values, and the results demonstrate the feasibility of the model in the development of GRDDS.

- M Khalid Khan.et.al., 40 Assessed the bioequivalence of tablets formulations of Clarithromycin 500mg each of test and reference products. A single post oral dose of each formulation was given to 14 male healthy volunteers. The study was conducted phase 1, open-label, randomized, complete two- way crossover designed with 7 days wash out period. The plasma concentration of clarithromycin was quantified by validated microbiological assay method. The precision of the method was evaluated using calibrated 14-hydroxy clarithromycin concentration was detected semi quantitatively as equivalent of clarithromycin /ml. The peak plasma concentrations of (3.63±0.80 ug/ml) and (3.31±0.35 ug/ml) was attained in about 1.42 hours and 1.49 hours for both test and reference Clarithromycin tablets respectively. The mean ± SD values for total area under the curve (AUC) were 22.07±4.90 and 20.16±2.35 h.mg/L for both test and reference tablets respectively. This study indicated that the differences in all the bioequivalence parameters for test and reference Clarithromycin formulations are statistically non-significant. Hence, both formulations are considered bioequivalent.

- Muralidhar Nama. et.al.,41 Developed the hydro dynamically balanced delivery system of Clarithromycin (CLA) which, after oral administration should have the ability to prolong gastric residence time with the desired in vitro release profile for the localized action in the stomach, in the treatment of Helicobacter pylori (H.pylori) mediated peptic ulcer. By applying wet granulation technique, floating tablets of Clarithromycin were prepared. The proportion of sodium bicarbonate was varied to get the least possible lag time, also the polymer part varied to get the desired release. In vivo radiographic studies were performed with Barium sulphate loaded formulation to justify the increased gastric residence time of the dosage form in the stomach, based on the floating principle. The formulation developed using 66.2% Clarithromycin, 12% HPMC K4M polymer, 8% sodium bicarbonate gave floating lag time less than 3 min with a floating time of 12 h, and an in vitro release profile very near to the desired release. X-ray studies showed the enhanced gastric residence time of the tablet to 220± 30 min. The mechanism of release of Clarithromycin from the floating tablets is anomalous diffusion transport

and follows zero order kinetics. In vivo radiographic studies suggest that the tablet has increased gastric residence time for the effective localized action of the antibiotic (Clarithromycin) in the treatment of H.pylori mediated peptic ulcer.

- Pradeep Kisan Nimase. et.al.,42 Developed a multiple-unit floating beads of clarithromycin from sodium alginate solution containing hydroxyl propyl methylcellulose (K100M) and sunflower oil using the technique of three variables at three levels (33) factorial design and twenty-seven possible batches were prepared. These beads were evaluated for entrapment efficiency, drug loading, buoyancy and in vitro drug release.
- All formulations showed floating lag time below 2 minutes and showed total floating duration more than 10 hours. The result of in-vitro dissolution studies revealed that the formulation F14 was showing sustained release pattern of clarithromycin. The release rate, entrapment efficiency, drug loading and buoyancy was greater with formulation containing 2 percent sodium alginate solution and 5 percent calcium chloride solution along with 5 ml sunflower oil.
- Nirav s sheth. et.al.,43 Designed a floating drug delivery to prolong the gastric residence time after oral administration at a particular site. It is useful for achieving controlled plasma level as well as improving bioavailability. With this objective, floating dosage form containing clarithromycin as drug was designed for the treatment of Helicobacter pylori infection. Tablets containing hydroxyl propyl methylcellulose (HPMC) drug and different additives were compressed using wet granulation. The study showed that tablet composition and mechanical strength have great influence on the floating properties and drug release. Incorporation of gas-generating agent together with polymer improved drug release, besides optimal floating lag time less than 30 sec, total floating time less than 6 hrs. The optimized formulation was obtained using 150mg of HPMC K4M gave floating lag time less than 30 sec with a total floating time greater than 6 hrs.
- Paruvathanahalli Siddalingam rajinithkanth.et.al., 44 Developed a stomach-specific drug delivery system for controlled release of clarithromycin for eradication of Helicobacter pylori (H. pylori). Floating-bioadhesive microspheres of clarithromycin (FBMC) were prepared by emulsification-solvent evaporation method using ethylcellulose as matrix polymer and Carbopol 934P as mucoadhesive polymer. The prepared microspheres were subjected to evaluation for particle size, incorporation efficiency, in vitro buoyancy, in vitro mucoadhesion and in vitro drug release characteristics. The prepared microspheres showed a strong mucoadhesive property with good buoyancy. The formulation variables like

polymer concentration and drug concentration influenced the in vitro drug release significantly in simulated gastric fluid (pH. 2.0). The in vivo H. pylori clearance efficiency of prepared FBMC in reference to clarithromycin suspension following repeated oral administration to H. pylori infected Mongolian gerbils was examined by polymerase chain reaction (PCR) technique and by a microbial culture method. The FBMC showed a significant anti-H. pylori effect in the in vivo gerbil model. It was also noted that the required amount of clarithromycin for eradication of H. pylori was significantly less in FBMC than from corresponding clarithromycin suspension. The results further substantiated that FBMC improved the gastric stability of clarithromycin (due to entrapment within the microsphere) and eradicated H. pylori from the sgastrointestinal tract more effectively than clarithromycin suspension because of the prolonged gastrointestinal residence time of the formulation.

- Mark A. Jacobson. et. al.,45 Developed a prophylaxis for AIDS-related disseminated Mycobacterium avium complex (dMAC) infection. Immediate-release (IR) clarithromycin tablets are dosed at 500 mg bid for these indications. A new extended-release (ER) tablet of clarithromycin has been developed and approved at a dosing interval of once every 24 hours for treatment of respiratory tract bacterial infections. However, the pharmacokinetics of clarithromycin ER in AIDS patients with or at risk for dMAC has not been previously investigated. They conducted a randomized, crossover trial in which 14 AIDS patients received clarithromycin ER, 1000 mg once daily, and clarithromycin IR, 500 mg bid, each for 1 week, with pharmacokinetic sampling at the end of each week. The mean of the individual AUC ratios for clarithromycin ER vs. IR was 1.09 (90% CI, 0.94–1.24). Adverse events were no more severe or frequent with clarithromycin ER than IR. Clarithromycin ER is a once-daily regimen that is as well tolerated as standard bid IR clarithromycin dosing and has average bioequivalence to the IR formulation in patients with AIDS.

- Eraha.et.al., 46 Explained a increased antibiotic chemical stability resulting from gastric pH changes induced by co administration of omeprazole. The chemical stability of clarithromycin, amoxycillin and metronidazole was investigated in aqueous solutions and in human gastric juice collected before and after a 7-day course of omeprazole. Amoxycillin, clarithromycin and metronidazole were prepared in buffered aqueous solutions of pH 1.0 to 8.0 and in gastric juice of pH 2.0 and 7.0. The gastric juice samples were obtained from fasted H. pylori-negative volunteers before and after they had received a 7-day course of

omeprazole. All the samples were incubated at 37°C and analyzed at intervals by HPLC. Amoxycillin, clarithromycin and metronidazole were stable in aqueous solutions of pH 4.0–7.0, pH 5.0–8.0 and pH 2.0–7.0, respectively. At pH 2.0, the degradation half-lives were 19.0 ± 0.2 h, 1.3 ± 0.05 h and 2200 ± 1100 h, respectively. In gastric juice samples of pH 2.0, the degradation half-lives were 15.2 ± 0.3 h, 1.0 ± 0.04 h and ³800 h, respectively. The half-lives of the drugs in the gastric juice samples of pH 7.0 were all >68 h. The co-administration of omeprazole with amoxycillin or clarithromycin is likely to increase the chemical stability of amoxycillin and clarithromycin in gastric juice. Clarithromycin degrades rapidly at normal gastric pH (1.0–2.0) but amoxicillin and metronidazole are sufficiently stable at this pH to maintain an antibacterial concentration in the stomach.

- Liandong Hu. et.al.,47 Developed and validated a method to prepare clarithromycin (CLM) microcapsules to mask the bitter taste and provide effective treatment, and evaluate the quality of microcapsules in detail, especially the in vitro and in vivo pharmacokinetics behavior. CLM microcapsules were prepared using ethyl cellulose as matrix material by an emulsion solvent diffusion method. The physicochemical property, in vitro release study, sensory test and stability test were evaluated. Self-made CLM dry suspension or conventional tablets containing 250 mg of CLM were orally administered with 250 mL of water. The plasma concentration was determined and the pharmacokinetic parameters were calculated by non-compartmental methods. Stable microcapsules could be prepared using ethyl cellulose as matrix material. The quality evaluation of prepared microcapsules was qualified, and the pharmacokinetic parameters of dry suspensions and conventional tablets were as following. Cmax were 1.32±0.62 and 1.40±0.58 μg ml-1 ; Tmax were 3.51±0.54 and 2.01±0.42 h ; AUC were 7.65±2.54 and 7.12±2.10 μg h ml-1. The preparation method is easy and applicable. The self-made CLM dry suspension containing microcapsules sufficiently alleviate the bitterness of commercial CLM dry suspension, but not decrease the bioavailability and have better effect for delaying drug release in healthy volunteers.

- Anish Kumar Gupta. et.al., 48 Developed a controlled release system targeting antibiotic delivery to the stomach. The hydrogels were synthesized by using chitosan, poly (acrylic acid) and poly (vinyl pyrrolidone) polymers crosslinked with glutaraldehyde and N,N'-methylenebisacrylamide. Interpenetrating polymeric network (IPN) hydrogels were prepared by varying the

concentration of crosslinking agent (glutaraldehyde). The amount of chitosan, poly (acrylic acid), poly (vinyl pyrrolidone) and N,N'-methylene bis acrylamide were kept constant in all formulations. The effect of glutaraldehyde concentration on the swelling and release characteristics were evaluated. Modalities used to assess the most optimal hydrogel formulation included high liquid chromatography, FTIR analysis, differential scanning calorimetry, swelling studies, in vitro drug release study, mucoadhesive study and scanning electron microscopy. The result showed that IPN hydrogels were greater in swelling, more mucoadhesive and released more drugs at lower pH values. Thus, it is believed that the antibiotic concentration in the stomach might be sustained through this formulation.

- Mark H. Gotfried. et.al.,49 Developed the steady-state concentrations of clarithromycin in plasma were compared with concomitant concentrations in epithelial lining fluid (ELF) and alveolar macrophages (AM) obtained from intrapulmonary samples during bronchoscopy and bronchoalveolar lavage (BAL).Concentrations of the major metabolite, 14 hydroxy clarithromycin, were also determined in plasma and AM. Forty-two healthy, non-smoking adult subjects (age: 18–54 years; 19 females, 23 males) received oral clarithromycin extended-release formulation (1000 mg once daily for five consecutive days). Bronchoscopy and BAL were carried out once in each subject at either 3, 6, 9, 12, 24 or 48 h after the last administered dose of clarithromycin. In addition, three subjects who did not take clarithromycin served as controls and underwent bronchoscopy at 0 hr. Drug concentrations in plasma, ELF, and AM were determined by high-performance liquid chromatography. Clarithromycin was extensively concentrated in ELF [range of mean (±S.D.) concentrations: 6.38 ± 3.92 to 11.50 ± 6.65 mg/L] and AM (127.0 ± 61.5 to 573.8 ± 309.3 mg/L) than simultaneous plasma concentration (0.75 ± 0.31 to 2.22 ± 0.72 mg/L). The ranges of mean (±S.D.) concentrations of 14-hydroxyclarithromycin in plasma and AM were 0.52 ± 0.29 to 0.80 ± 0.31 mg/L and 22.1 ± 13.5 to 49.5 ± 16.2 mg/L, respectively. Conclusions: Once-daily dosing of extended-release formulation clarithromycin 1000 mg produced significantly ($P < 0.05$) higher steady-state concentrations of clarithromycin in ELF (2–14 times) and AM (50–700 times) compared to simultaneous plasma concentrations throughout the 24 h period after drug administration. The 14-hydroxy metabolite of clarithromycin achieved significantly ($P < 0.05$) higher steady-state concentrations in AM (18–180 times) compared with concurrent plasma concentrations.

- GK.Tripathi.et.al., 50 Developed a pH-sensitive controlled release formulation of clarithromycin in oil-entrapped calcium pectinate microgel bead.

Pectin-based oil-entrapped microgel beads were prepared by ionic gelation technique. The gel beads were formed instantly after adding the liquid formulation mixture drop wise into calcium chloride solution. The beads were optimized by coating with ethyl cellulose solution and then evaluated for their diameter, floating lag time, encapsulation efficiency and drug release. Particle size, encapsulation efficiency and buoyancy were significantly affected by the concentration of the polymer and calcium chloride. The formulation exhibited sustained release profile and was best fitted to the Peppas model with $n < 0.45$. Ethyl cellulose-coated formulation batch, C16, was the most suitable controlled formulation with drug release of 65 ± 2.61 % in 8 h. An ethyl cellulose-coated formulation with potential for sustained delivery of clarithromycin in the acidic region of the gastrointestinal tract was successfully developed.

- M. Lohitnavy. et.al., 51 Assessed a average bioequivalence of two immediate released tablet formulations of 500-mg clarithromycin tablets in 24 healthy Thai male volunteers. In a randomized, single dose, fasting state, two-period, crossover study design with a 1-week washout period, each subject received a 500-mg clarithromycin tablet. Plasma samples were collected over a 24-hour period after oral administration and were analyzed by using a validated method using high performance liquid chromatography with electrochemical detection. Pharmacokinetic parameters were determined by using noncompartmental analysis. The time to reach the maximal concentration (tmax, h), the peak concentration (Cmax, ng/mL), and the area under the curve (AUC0 − ∞, ng.h/mL) of the Reference and Test formulations were 2.0 ± 0.8 vs. 2.2 ± 0.9, 2793 ± 1338 vs. 2642 ± 1344, and 17912 ± 7360 vs. 17660 ± 7992, respectively. Relative bioavailability was 0.99. The 90% confidence interval of Cmax and AUC0 − ∞ were 82.6–112.1% and 84.7–112.0%. Bioequivalence between the Test and Reference formulation can be concluded.

- Suman Ramteke. et.al., 52 Prepared and evaluated the oral mucoadhesive sustained release nanoparticles of clarithromycin in order to improve patient compliance by simplifying its administration, improving its therapeutic effect and reducing its dose related side effect. Clarithromycin containing gliadin nanoparticles were prepared by desolvation method using pluronic F-68 as a stabilizing agent. The results showed that this method is reproducible, very easy and led to the efficient entrapment of drug as well as formation of spherical particles ranging from 250-500 nm. Some process variables like effect of gliadin concentration and effect of surfactant were also evaluated with respect to their %

drug entrapment and % yields. The maximum % drug entrapment and % yield were about 73 and 88%, respectively. The sustained release behavior of gliadin nanoparticles were evaluated both in phosphate buffer saline (pH 7.4) and simulated gastric fluid (pH 1.2), respectively at 37±1oC. Their mucoadhesive properties were determined by in vivo and in vitro methods. The shelf life of prepared nanoparticles was determined by storage at various temperatures while assessed in simulated gastric fluid (pH1.2) with and without enzyme.

- Md. Nehal Siddiqui, et.al.,53 Developed the fast dissolving tablet (FDT) with improved patient compliance and convenience. FDTs are solid dosage forms which dissolve rapidly in saliva without chewing and additional water. FDTs overcome the disadvantages of conventional dosage form especially dysphagia (difficulty in swallowing) in pediatric and geriatric patients.
- This review includes ideal properties, characteristics, challenges in formulation, suitability of drug candidates, various technologies developed for FDT, patented technologies, evaluation methods and various marketed products.
- Pradeep Kisan Nimase. et.al.,54 Developed a Multiple-unit floating beads of clarithromycin from sodium alginate solution containing hydroxypropyl methylcellulose (K100M) and sunflower oil using the technique of three variables at three levels (33) factorial design and twenty-seven possible batches were prepared. These beads were evaluated for entrapment efficiency, drug loading, buoyancy and in vitro drug release. All formulations showed floating lag time below 2 minutes and showed total floating duration more than 10 hours. The result of in-vitro dissolution studies revealed that the formulation F14 was showing sustained release pattern of clarithromycin. The release rate, entrapment efficiency, drug loading and buoyancy was greater with formulation containing 2 percent sodium alginate solution and 5 percent calcium chloride solution along with 5 ml sunflower oil.
- Shashikant D. Barthate. et.al.,55 Designed a floating matrix tablets to prolong the gastric residence time after oral administration, at a particular site and controlling the release of drug especially useful for achieving controlled plasma level as well as improving bioavailability. With this objective, controlled release floating tablets of clarithromycin were formulated by using D-optimal mixture design for the treatment of Helicobacter pylori. The amount of HPMC K4M: HPMC K100LV in 1:1 ratio (X1), amount of Na-CMC (X2) and amount of sodium bicarbonate (X3) were selected as independent variables and percentage drug release at 3 h (Y1), percentage drug release at 6h(Y2), percentage drug release at

12h (Y3) and total floating lag time (Y4) as dependent variables. Tablets containing HPMC K4M and HPMC K100LV, drug and different additives were prepared by wet granulation. The tablet composition and mechanical strength have great influence on the floating properties and drug release. Optimization of the evaluating parameters with Design expert software was employed to generate optimized formulation and criteria of desirability was employed. The optimized formulation was obtained with HPMC K4M: HPMC K100LV in 1:1 ratio (125.428 mg), Na-CMC (40.256 mg) and sodium bicarbonate (34.316 mg). The in vitro release data showed that the drug release follows zero-order release kinetics.

- Bathini Sree Tejaswi. et.al.,56 Developed a stomach-specific drug delivery system for controlled release of clarithromycin for eradication of Helicobacter pylori (H. pylori). Floating Microspheres of clarithromycin (FMC) were prepared by Solvent Evaporation Technique using ethyl cellulose as a polymer. The prepared microspheres were subjectedto evaluation for particle size, incorporation efficiency, in vitro buoyancy, in vitro drug release characteristics and stability studies. These microspheres showed good buoyancy. The formulation variables like polymer concentration and drug concentration influenced the in vitro drug release significantly in simulated gastric fluid (pH 2.0). It was also noted that the required amount of clarithromycin for eradication of H. pylori was significantly less in FMC than from corresponding clarithromycin suspension. About 82% of the prepared microspheres floated in hydrochloric acid buffer solution for 12h. 71% of the clarithromycin contained in the microspheres were released within 12 h in a sustained manner. These results suggest that FMC will be a promising drug delivery system for the treatment of H. pylori infection.

- Venkateswaramurthy N. et.al., 57 Designed a mucoadhesive microspheres containing Clarithromycin as an anti-H. pylori agent to deliver the drug specifically to mucus layer where H.pylori resides and evaluate the effectiveness of the mucoadhesive microspheres for H. pylori eradicationtherapy. Microspheres were prepared by using Eudragit RL100 as matrix and Carbopol 974P and Hydroxy propyl methyl cellulose K4M as mucoadhesive polymer. The microspheres prepared by emulsion solvent evaporation technique. The prepared microspheres were evaluated with respect to the particle size, production yield, encapsulation efficiency, shape and surface properties, mucoadhesive property, In-vitro drug release and suitability for anti Helicobactor pylori effect. The preliminary results show great promise for this delivery strategy in the treatment of H. Pylori infection

IV. MATERIALS AND METHODS

4.1. LIST OF MATERIALS USED

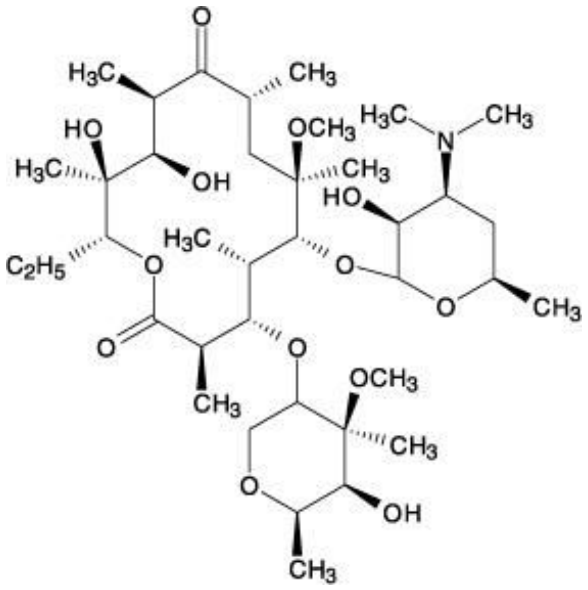
Table No. 3: List of materials used

S. No.	Materials	Manufacturers/Suppliers
1	Clarithromycin	Anuh pharma Pvt.Ltd.
2	Croscarmellose sodium	Signet chemicals pvt.,Ltd
3	Colloidal silicon dioxide	Cabor sanmar Ltd
4	Ethyl cellulose	The dow chemical company
5	Ethyl vanillin	Firemenich, Switzerland.
6	Hydroxy propyl cellulose	Aqualon
7	Pregelatinised starch	DMV Fonterra excipients,USA.
8	Microcrystalline cellulose PH 101	Signet chemicals pvt.,Ltd
9	Microcrystalline cellulose PH 102	Weiming Pharmaceuticals
10	Propylene glycol	Clariant
11	Povidone IP (K-30)	Nanberg India co.
12	Isopropyl alcohol	Deepak Fertilizers
13	Magnesium stearate	Vijlak Pharma
14	Talc	Luzanac pharma
15	Titanium dioxide	BASF
16	Qunoline yellow lake	Satyasta chemicals, kanpur

4.2. DRUG PROFILE

CLARITHROMYCIN [64] :

Structure :



Molecular formula : $C_{38}H_{69}NO_{13}$

Molecular weight : 748.95

Chemical name : 6-O-Methyl erythromycin A.

Therapeutic category : Semi synthetic Macrolide Antibiotic.

Active metabolite : Clarithromycin,14-hydroxyclarithromycin.

Description : White to off-white, Non-hygroscopic crystalline powder.

Melting point : 217-220^{o}C

Solubility : Practically insoluble in water,Soluble in acetone, Slightly soluble in methanol, ethanol and acetonitrile.

Dos **:** 250-500 mg BD 7-14 days

Plasma half-life **:** 2-3 hours

Steady state peak plasma concentrations **:** Attained within 3-4 days.

Elimination half-life **:** 3-7 hours for clarithromycin, 5-9 hours for 14-OH clarithromycin.

Absolute bioavailability **:** Approx.50%

clearance **:** Approximates normal GFR.

Shelf life **:** 36 months

Impurities [65] **:** Clarithromycin N-oxide
N-Desmethyl clarithromycin (EP Impurity D)
N-Desmethyl erythromycin A
N-Formyl clarithromycin (EP Impurity H)

PHARMACOLOGY [9,10,11,12,60,61,62]

MECHANISM OF ACTION:

Macrolides are protein synthesis inhibitors. The mechanism of action of macrolides is inhibition of bacterial protein biosynthesis, the drugs act by binding to cell membranes and causing changes in protein function and they are thought to do this by preventing peptidyltransferase from adding the peptidyl attached to t-RNA to the next amino acidas well as inhibiting ribosomal translocation. Another potential mechanism is premature dissociation of the peptidyl-tRNA from the ribosome.

Macrolide antibiotics do so by binding reversibly to the P site on the subunit 50S of the bacterial ribosome. Macrolides inhibit the translocation of the growing peptide chain from A site to P site. Hence A site is not available for binding of next aminoacid (brought by t-RNA).This action is mainly

bacteriostatic, but can also be bactericidal in high concentrations. Macrolides tend to accumulate within leukocytes, and are, therefore, transported into the site of infection.

PHARMACOKINETICS:

ABSORPTION &BIOAVAILABILITY :

- Clarithromycin is acid stable drug and it is rapidly absorbed from the gastrointestinal tract after oral administration.
- The absolute bioavailability of Clarithromycin was approx. 50% because of hepatic metabolism.
- For a single 500 mg dose of clarithromycin, food slightly delays the onset of clarithromycin absorption.
- Absorption of clarithromycin was increased by food.
- It increases the peak time from approx. 2-2.5 hours.
- Food also increases the clarithromycin peak plasma concentration by about 24%, but does not affect the extent of clarithromycin bioavailability.
- Food does not affect the onset of formation of anti microbial active metabolite,14-hydroxy clarithromycin or peak plasma concentration.
- Food slightly decrease the extent of metabolite formation, indicated by an 11% decrease in area under the plasma concentration time-curve (AUC).
- Therefore, clarithromycin tablets may be given without regard to food.
- In non-fasting healthy human subjects (males and females), peak plasma concentration, were attained within a 2-3 hours after oral dosing.
- Steady-state concentration of clarithromycin was attained within 3-4 days.
- With a 500mg every 8-12 hours dosing, the peak steady state concentration of the 14-OH clarithromycin is slightly higher (up to 1mcg/ml) and its elimination half life is about 7-9 hours.The steady-state concentrations of clarithromycin and 14-OH clarithromycin observed by administration of 500 mg doses of clarithromycin

every 12 hours to adult patients with HIV infection were similar to those observed in healthy volunteers.

- The steady-state concentration of clarithromycin in subjects with impaired hepatic function did not differ from those normal subjects.
- However, 14-OH clarithromycin concentration was lower in hepatically impaired subjects.

DISTRIBUTION:

- Clarithromycin and 14-OH clarithromycin is well distributed to all body tissues, middle ear and fluids except CNS.
- But no data is available for the cerebra spinal fluid (CSF) penetration.
- It achieves high intracellular concentrations throughout the body.
- Because of higher intracellular concentrations, tissue concentrations are higher than serum concentration.
- It also diffuses into the prostatic fluid.
- Protein binding ranges from 40-80% at therapeutic level and it is concentration independent.
- It has unique characteristics of accumulation in macrophages.
- It mainly concentrates in the liver.
- Inflammation allows for greater tissue penetration.
- When clarithromycin 500 mg is given 3 times daily, the clarithromycin plasma concentration is increase with respect to the 500 mg twice-daily dosage.
- Clarithromycin provides tissue concentration that is several times higher than circulating drug levels. Increased levels have been found in both tonsillar and long tissue.
- It also penetrates the gastric mucus, levels of clarithromycin in gastric mucus and gastric are higher, when clarithromycin is co-administrated with omeprazole than when clarithromycin is administrated alone.

METABOLISM:

- Clarithromycin is metabolized in the liver to several metabolites.
- The primary metabolic pathways undergoes oxidative N-demethylation and hydroxylation at the 14-position to form an active metabolite 14-OH clarithromycin, which gives a antibiotic activity.
- Partially metabolized through hepatic via CYP3A4.
- Metabolic is saturable, resulting non-linearity pharmacokinetics and longer half-life are observed after larger doses.
- Clarithromycin is interference with metabolism of drugs such as theophylline and carbamazepine.

➢ **EXCREATION:**

- Clarithromycin and its metabolites are eliminated by the kidneys as well as the liver.
- The amount of clarithromycin excreted unchanged in the urine ranges from 20-40%, and it depends on the dose and the formulation.
- Additionally, 14-OH clarithromycin is major excretory metabolite, it accounts for 10-15% of a dose excreted in the urine as 14-OH clarithromycin.
- Most of the remainder of the dose is eliminated in faeces, primarily via the bile, 5-10% of the parent drug is recovered from the faeces.
- With 500 mg b.i.d, daily dosing urinary excretion is greater (approx 36%).
- The elimination half life is 3-4 hours for clarithromycin for 250 mg and 5-9 hours for 14-OH clarithromycin.
- The elimination half-life of clarithromycin was about 5-7 hours with 500mg administered for every 8-12 hours.
- It is recommended that the dosage of this drug be adjusted in patients with compromised renal function.

➢ PHARMACODYNAMICS:

- Clarithromycin is semi synthetic derivative of erythromycin A. It exerts a antibacterial activity by binding to the 50s ribosomal sub unit of susceptible bacteria and suppresses protein synthesis.

- It is highly potent against a wide variety of aerobic and anaerobic gram-positive and gram-negative organisms. The minimum inhibitory concentrations (MICs) of Clarithromycin are generally two-fold lower than the MICs of erythromycin.
- It is usually bacteriostatic, but may be bacteriocidal depending on the organism and the drug concentration.
- Clarithromycin is usually active against the following organisms in vitro: Gram-positive bacteria: staphylococcus aureus, streptococcus pneumonia. Gram-negative bacteria: Haemophilus influenza, Neisseria gonorrhoeae, Helicobacter pylori. Other organisms: Mycobacterium avium.

USES

- It can be used in the treatment of Acute otitis media (AOM), Pharyngitis and Tonsillitis, respiratory tract infections, skin infections, Helicobacter pylori infections, duodenal ulcer disesase, Bartonella infections, cyprosporidiosis, Lyme disease, Mycobacterial infections, Toxoplasmosis, Prevention of bacterial endocarditis.
- It can be used as an alternative to penicillin in patients allergic to penicillin.
- It can be used in the treatment of Atypical pneumonia, legionnaires pneumonia, whooping cough, streptococcal infections, staphylococcus infections, diphtheria, syphilis, gonorrhea, campylobacter gastroenteritis, tetanus, anthrax, topical infections, etc.,

➢ METHOD OF ADMINISTRATION

Patients with respiratory tract/skin and soft tissue infections.

Adults: The usual dose is 250 mg twice daily although this may be increased to 500mg twice daily in severe infections. The usual duration of treatment is 6 to 14 days.

Children older than 12 years: As for adults.Use of clarithromycin 500 mg tablets are not recommended for children younger than 12 years.

Eradication of *H. pylori* in patients with duodenal ulcers (Adults)

The usual duration of treatment is 6 to 14 days.

Triple Therapy:

i) Clarithromycin (500mg) twice daily and lansoprazole 30mg twice daily should be given with amoxycillin 1000mg twice daily.
ii) Clarithromycin (500mg) twice daily and lansoprazole 30mg twice daily should be given with metronidazole 400mg twice daily.
iii) Clarithromycin (500mg) twice daily and omeprazole 40mg daily should be given with amoxycillin 1000mg twice daily or metronidazole 400mg twice daily.
iv) Clarithromycin (500mg) twice daily should be given with amoxycillin 1000mg twice daily and omeprazole 20mg daily.

Dual Therapy:

The usual dose of Clarithromycin is 500 mg three times daily. Clarithromycin should be administered with oral omeprazole 40 mg once daily for 14 or 28 days.

- Clarithromycin may be given without regard to meals, as food does not

affect the extent of bioavailability.

- **OVER DOSE:**

  - The large amounts of clarithromycin can produce gastro-intestinal symptoms.
  - It shows altered mental status, paranoid behaviour, hypokalemia and hypoxemia.

INDICATIONS:

It is used in the treatment of pharyngitis/tonsillitis acute maxillary sinusitis, acute bacterial exacerbation of chronic bronchitis, commonly acquired pneumonia, uncomplicated skin infections, disseminated mycobacterial infections, Helicobacter pylori and duodenal ulcer disease when used in combination with amoxicillin and lansprazole or omeprazole; Helicobacter pylori and duodenal ulcer disease when used in combination with omeprazole or ranitidine bismuth citrate, prevention of mycobacterium avium complex (MAC) disease in patients with HIV infections.

CONTRAINDICATIONS:

- Clarithromycin is contra-indicated in patients with known hypersensitivity to macrolide antibiotic drugs.
- Clarithromycin and ergot derivatives should not be co-administered.
- Concomitant administration of clarithromycin is contraindicated in some drugs like: cisapride, pimozide and terfenadine. This may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and Torsade de Pointes.

➢ WARNINGS AND PRECAUTIONS:

- Clarithromycin is excreted by the liver and kidney. Caution should be exercised in administering this antibiotic to patients with impaired hepatic or renal function.
- Prolonged or repeated used of clarithromycin may result in an overgrowth of non-susceptible bacteria or fungi.
- If super-infection occurs, clarithromycin should be discovered.
- *H. pylori* organisms may develop resistance to clarithromycin in some patients.
- Deaths have been reported in some such patients.

ADVERSE EFFECTS:

Gastrointestinal: abdominal cramps, nausea, diarrhea, anorexia, pancreatitis

Genitourinary: vulvovaginal candidiasis, renal failure

Cardiovascular System: prolongation of QT interval

Hepatic: hepatotoxicity, jaundice

Hematologic: eosinophilia, thrombocytosis, lymphopenia

Central Nervous System: headache, fatigue

Endocrine/Metabolic: hyperglycemia

Dermatologic: itching, nail discoloration

Others: reversible hearing impairment.

➢ DRUG INTERACTIONS:

Clarithromycin inhibit the hepatic metabolism and thereby rise the plası carbamazepine, terfenadine, theophylline, digoxin, valproate, and warfarin resu in toxicity due to these dugs.

PHARMACEUTICAL EXCIPIENT PROFILE[66]

CROSCARMELLOSE SODIUM

Synonyms:

Ac-Di-Sol; crosslinked carboxymethylcellulose sodium; Explocel; Primellose; Vivasol; Solutab.

Empirical formula: croscarmellose sodium is a crosslinked polymer of carboxymethylcellulose sodium.

Description: Croscarmellose sodium occurs as an odourless, white or greyish-white powder.

Functional category: Tablet and capsule disintegrant.

Solubility: It is insoluble in water, but rapidly swells to 4-8 times its original volume on contact with water and practically insoluble in acetone, ethanol and toluene.

TYPICAL PROPERTIES:

pH – 5.0 to 7.0 in aqueous dispersions.

Density – 1.543 g/cm^3

Loss on drying - ≤ 10%

Content of water-soluble material – 1.0 to 10%

Settling volume – 10 to 30 ml.

Particle size distribution – NMT 2% retained on a #200 mesh

NMT 10% retained on a #325 mesh

PHARMACEUTICAL APPLICATIONS:

Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets and granules.When used in wet granulations, croscarmellose sodium should be added in both the wet and dry stages of the process so that the wicking and swelling ability of the disintegrant is best utilized.Concentrations of up to 5%w/w of croscarmellose sodium may be used as a tablet disintegrant although normally 2% w/w is used in tablets prepared by direct compression and 3%w/w in tablets prepared by a wet granulation process.

Use	**Concentration (%)**
Disintegrant in capsules	10-25%
Disintegrant in tablets	0.5-5.0%

INCOMPATIBILITIES:

The efficacy of disintegrants, such as croscarmellose sodium, may be slightly reduced in tablet formulations prepared by either the wet granulation or direct compression process that contain hygroscopic excipients such as sorbitol.

Croscarmellose sodium is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury and zinc.

MICROCRYSTALLINE CELLULOSE

Non proprietary Names : Microcrystalline cellulose, cellulosum microcrystallinum.

Synonyms : Avicel PH, celex, cellulose gel, hellulosum microcrystallinum, Emcocel, Fibrocel, Pharmacel, Vivace, E460.

Empirical formula: $(C_6H_{10}O_5)_n$, where n =220.

Molecular weight **:** Approx**.**36000

Applications

It is used primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet granulation and direct compression processes. It also has some lubricant, anti-adherent, and disintegrating properties, which make it useful in tableting.

Description

Microcrystalline cellulose is purified, partially depolymerized cellulose that occurs as white, odourless, tasteless, crystalline powder composed of porous particles. It is commercially available in various particle sizes and moisture grades that have different properties and applications.

Typical Properties **:** pH – 5.0 to 7.5

Density (true) – 1.512 to 1.668 g/cm^3

Angle of repose – 34.4˚

Melting point – Chars at 260 to 270˚C

Moisture content - <5% w/w; hygroscopy.

Pharmaceutical applications of Microcrystalline cellulose:

Use	**Concentration (%)**
Adsorbent	20-90
Anti adherent	5-20
Capsule	20-90

binder/diluents	
Tablet disintegrant	5-15
Tablet binder/diluents	20-90

Table no 4: Properties of some commercially available grades of microcrystalline cellulose:

Grade	***Nominal mean particle size (µm)***	***Particle size analysis***		***Moisture content (%)***
		Mesh size	***Amount retained(%)***	
Avicel PH-101	*50*	*60* *200*	*≤1.0* *≤30.0*	*≤5.0*
Avicel PH-102	*100*	*60* *200*	*≤8.0* *≥45.0*	*≤5.0*
Avicel PH-103	*50*	*60* *200*	*≤1.0* *≤30.0*	*≤3.0*
Avicel PH-105	*20*	*400*	*≤1.0*	*≤5.0*
Avicel PH-112	*100*	*60*	*≤8.0*	*≤1.5*
Avicel PH-113	*50*	*60* *200*	*≤1.0* *≤30.0*	*≤1.5*
Avicel PH-200	*180*	*60* *100*	*≥10.0* *≥50.0*	*≤5.0*
Avicel PH-301	*50*	*60* *200*	*≤1.0* *≤30.0*	*≤5.0*
Avicel PH-302	*100*	*60* *200*	*≤8.0* *≥45.0*	*≤5.0*

Incompatibilities: Incompatible with strong oxidizing agents.

Safety:

Microcrystalline cellulose is widely used in oral pharmaceutical formulations and food products and is generally regarded as a relatively nontoxic and nonirritant material.

Microcrystalline cellulose is not absorbed systemically following oral administration and thus has little toxic potential. Consumption of large quantities of cellulose may have a laxative effect, although this is unlikely to be a problem when cellulose is used as an excipient in pharmaceutical formulations. Deliberate abuse of formulations containing cellulose, either by inhalation or by injection, has resulted in the formation of cellulose granulomas.

HYDROXY PROPYL CELLULOSE

Non properties

Names : Hydroxypropyl cellulose,hydroxyl propyl cellulosum

Synonyms : Cellulose, Hydroxypropyl ether, E463, hydroxypropylcellulosum; Hyprolose, Klucel.

Molecular weight : Ranges from 50000 to 1250000

Description: Hydroxypropyl cellulose is a white to slightly yellow-coloured, odourless and tasteless powder.

Functional category: Coating agent; emulsifying agent; stabilizing agent; suspending agent; tablet binder; thickening agent; viscosity-increasing agent.

Solubility:

Freely soluble in water below 38˚C, forming a smooth, clear, colloidal solution. In hot water, it is insoluble and is precipitated as a highly swollen floc at a temperature between 40 and 45˚C. Soluble in many cold or hot polar organic solvents such as dimethyl formamide, dimethyl sulfoxide, dioxane, ethanol (95%), methanol, propan-2-ol (95%) and propylene glycol.

Typical properties:

- pH – 5.0 to 8.5 (1% w/w aqueous solution)
- Density – 0.5 g/cm^3
- Melting point – Softens at 130˚C, chars at 260-275˚C.
- Loss on drying - ≤ 5.0%

Pharmaceutical applications:

Hydroxypropyl cellulose is primarily used in tableting as a binders, film coating, and extended release matrix former. It is used as a binder, when it is used in 2-6% in both wet and dry granulation processes. The release rate of drug increases with decreasing viscosity of Hydroxypropyl cellulose. 5% is used in film coated solution. stearic or palmitic acid may be added to ethanolic Hydroxypropyl cellulose solutions as plastcizers. A low subistituted Hydroxypropyl cellulose is used as a tablet disintegrant.

Use	**Concentration (%)**
Extended release matrix former	15-35%
Tablet binder	2-6%
Tablet film coating	5%

Incompatibilities:

Hydroxypropyl cellulose in solution demonstrates some incompatibilities with substituted phenol derivatives, such as methylparaben and propylparaben. The presence of anionic polymers may increase the viscosity of Hydroxypropyl cellulose solutions. The compatibility of Hydroxypropyl cellulose with inorganic salts varies depending upon the salt and its concentration. It may not tolerate high concentrations of other dissolved materials.

Safety:

The WHO has specified an acceptable daily intake for Hydroxypropyl Cellulose of up to 1500 mg/kg body-weight. Excessive consumption of Hydroxypropyl Cellulose may have a laxative effect.

LD50 (rat, IV): 0.25 g/kg

LD50 (rat, oral): 10.2 g/kg

PREGELATINIZED STARCH

Nonproprietary Names: Starch, pregelatinized, pregelatinized starch.

Synonyms **:** compressible starch, instastarch, starch 1500, pharma-gel, prejel.

Chemical name **:** pregelatinized starch

Molecular formula **:** $(C_6H_{10}O_5)_n$,where n=300-1000

Description :

Pregelatinised starch occurs as a moderately coarse to fine, white to off-white colored powder. It is odorless and has a slight characteristic taste.

Typical properties **:** pH – 4.5-7.0

Density (true) – 1.516 g/ml^3

Angle of repose- $40^{o}.7^{''}$

Solubility:

It is practically insoluble in organic solvents. Slightly soluble in coldwater,depending on the degree of pre gelatinization**.**

Applications:

Pregelatinised starch is a modified starch used in oralcapsule and tablet formulations as a binder, diluent anddisintegrant. In comparison to starch, grades of Pregelatinisedstarch may be produced with enhance flow and compressionCharacteristics such that the Pregelatinised material may be usedas a tablet binder in dry-compression or direct compression processes. In such processes, Pregelatinised starch is self lubricating. However, when it is used with other excipients it may be necessary to add a lubricant to a formulation. Although magnesium Stearate 0.25% w/w is commonly used for this purpose, concentrations greater than this may have adverse effects on tablet strength and dissolution. Therefore, stearic acid is generally the preferred lubricant with pregelatinised starch.

Use	***Concentration (%)***
Tablet binder (wet granulation)	*5–75*
Tablet disintegrant	*5–20*
Diluent (hard gelatin capsules)	*5–10*
Tablet binder (direct compression)	*5–10*

POVIDONE

Nonproprietary Names : Povidone (BP, JP, PhEur, USP)

Synonyms :

Kollidon, Poly [1-(2-oxo-1-pyrrolidinyl) ethylene],polyvidone, polyvinylpyrrolidone,

povidonum, Povipharm, PVP, 1- vinyl-2-pyrrolidinone polymer.

Molecular Weight: 2500–3000000

Description :

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless,hygroscopic powder.

Solubility :

Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol and water.

Practically insoluble in ether, hydrocarbon and mineral oil.

Functional Category :

Disintegrant, dissolution enhancer, suspending agent and tablet binder.

Applications :

In tableting, Povidone solutions are used as binders in wet-granulation processes. It is used as a solubilizer in oral and parenteral formulations and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms. Povidone solutions may also be used as coating agents or as binders. Additionally it is used as a suspending, stabilizing or viscosity-increasing agent in a number of topical, oral suspensions and solutions. The solubility of a number of poorly soluble active drugs may be increased by mixing with Povidone.

Incompatibilities :

It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, Phenobarbital, tannin and other compounds.

MAGNESIUM STEARATE

Synonyms: Magnesium octadecanoate, octadecanoic acid, Magnesium salt and stearic acid.

Description:

It occursas a fine, white precipitated or milled impalpable powder with a faint odour and a characteristic taste.

Functional categories: Tablet and capsule lubricant.

Molecular weight: 591.34

Solubility:

Practically insoluble in ethanol, ether and water, slightly soluble in warm benzene and warm ethanol (95 %).

Melting point : 117-150°C

Stability and storage conditions:

It is stable and should be stored in a well-closed container in a cool, dry place.

Incompatibilitie:

Incompatible with strong acids, alkalis and iron salts.

Applications:

It is primarily used as a lubricant in tablet and capsules in concentrations between 0.25 % and 5 %. It is widely used in cosmetic and food industry.

ISOPROPYL ALCOHOL

Synonyms :

Dimethyl carbinol, isopropanol, petrohol, 2-propanol and secpropyl alcohol.

Molecular weight **:** 60.1

Functional category **:** Disinfectant, solvent.

Description :

Isopropyl alcohol is a clear, colorless, mobile, volatile and flammable liquid with

Characteristic spirituous odor, resembling that of a mixture of ethanol and acetone.

It has a slightly bitter taste.

Typical properties

Antimicrobial activity:

Isopropyl alcohol is bactericidal; at concentrations greater than 70% v/v it is a more effective antibacterial preservative than ethanol (95%).

Boiling Point **:** 82.4ºC.

Freezing point **:** **-**89.58ºC

Melting point: **-**88.58ºC

Solubility:

Miscible with benzene, chloroform, ethanol (95%), ether, glycerin and water.

Soluble in acetone and insoluble in salt solutions.

Stability and storage :

Isopropyl alcohol should be stored in an airtight container in a cool, dry place.

Incompatibilities:

Incompatible with oxidizing agents such as hydrogen peroxide and nitric acid, which

cause decomposition.

TALC

Nonproprietary Names : Purified talc, Talc,Talcum

Synonyms:

Magsil Star, powdered talc, hydrous magnesium calcium silicate, hydrous magnesium silicate, purified French chalk, Purtalc, soapstone.

Chemical name : Talc

Molecular formula: $Mg_6 (Si_2O_5)_4(OH)_4$.

Description :

Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

Functional Category: Anticaking agent, glidant, tablet and capsule diluents, tablet and capsule lubricant.

Typical properties :pH = 7–10 Moisture content: Talc absorbs insignificant of water at 25^{o}C and relativehumidities up to about 90%.

Solubility:

Practically insoluble in dilute acids and alkalis, organic solvents, and water.

Applications:

Talc was once widely used in oral solid dosage formulations as a lubricant and diluents. However, it is widely used as a dissolution retardant in the development of controlled-release products. Talc is also used as a lubricant in tablet formulations. In a novel powder coating for extended-release pellets and as an adsorbent. In topical preparations, is used as a dusting powder.

Use	***Concentration (%)***
Dusting powder	*5.0–30.0*
Glidant and tablet lubricant	*1.0–10.0*
Tablet and capsule diluent	*90.0–99.0*

Incompatibilities : Incompatible with quaternary ammonium compounds.

Stability :

Talc is a stable material and may be sterilized by heating at160^{o}C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation. Talc should be stored in a well-closed container in a cool, dry place.

ETHYL VANILLIN

Nonproprietary Names **:** Ethyl vanillin.

Synonyms **:** Bourbonal, ethylporta ethyl protocatechuic aldehyde, vanilla.

Chemical name **:** 3-ethoxy-4-hydroxy benzaldehyde

Molecular formula **:** $C_9H_{10}O_3$

Molecular Weight: 166.18

Description : white or slightly yellowish crystals with a characteristic intense vanilla odor and flavor.

Typical properties **:** Density(bulk):1.05

Melting point: 76-78^{o}C

Boiling point : 285^{o}C

Solubility :

In chloroform, it is freely soluble. In glycerin, it is soluble. In propylene glycol, it is soluble.

Functional Category **:** Flavoring agent

Applications :

Ethyl vanillin is used as an alternative to vanillin i.e., as a flavoring agent in foods,

Beverage sand pharmaceuticals. It is also used in perfumery. It possesses a flavor and odor approximately three times as intense as vanillin, Hence the quality of material necessary to produce an equivalent vanilla flavor may be reduced, causing less discoloration to a formulation and potential savings in material costs However,exceeding certain concentration limits may impart an unpleasant, slightly bitter taste to a product due to the intensity of the ethyl vanillin flavor.

Incompatibilities :

Ethyl vanillin is unstable in contact with iron or steel forming a red-colored, flavorless compound.

Stability :

Stored in a well-closed container, protected from light, in a cool, dry, place.

PROPYLENE GLYCOL

Nonproprietary Names : Propylenglycolum, Propylene glycol

Synonyms **:** Dihydroxypropane, 2-hydroxypropanol, methylethylene glycol,
methyl glycol, propane-1,2-diol.

Chemical name **:** 1,2-Propanediol

Molecular weight **:** 76.09

Description:

Propylene glycol is a clear, colorless, viscous, practically odorless liquid with a sweet, slightly acrid taste resembling that of glycerin.

Molecular formula **:** $C_3H_8O_2$

Typical properties **:**Boiling point: 188^oC

Density: 1.038 g/cm^{3}at 20^oC

Melting point: -59^oC

Solubility :

Miscible with acetone, chloroform, ethanol (95%) glycerin, and water; soluble at 1 in 6 parts of ether, not miscible with light mineral oil or fixed oils, but it will dissolve in some essential oils.

Functional Category :

Antimicrobial preservative, disinfectant, humectants, Plasticizer, solvent, stabilizer for vitamins, water-miscible co solvent.

Applications :

Propylene glycol has become widely used as a solvent, extractant, and preservative in a variety of parenteral and nonparenteral pharmaceutical formulations. It is a better general solvent than glycerin and dissolves a wide variety of materials, such as corticosteroids, phenols, sulfa drugs, barbiturates, vitamins (A and D), most alkaloids and local anasthetics. As an antiseptic it is similar to ethanol and against molds it is similar to glycerin and only slightly less effective than ethanol. Propylene glycol is commonly used as a plasticizer in aqueous film-coating formulations.

Incompatibilities:

Propylene glycol is incompatible with oxidizing reagent. Such as potassium permanganate.

Stability:

At cool temperatures, propylene glycol is stable in a well-closed container, but at high temperatures, in the open, it tends to oxidize, giving rise to products such as propionaldehyde, lactic acid, pyruvic acid, and acetic acid. Propylene glycol is chemically stable when mixed with ethanol (95%), glycerin, or water aqueous solutions may be sterilized by autoclaving.

Storage:

Propylene glycol is hygroscopic and should be stored in a well-closed container, protected from light, in a cool, dry place.

QUINOLINE YELLOW LAKE

Synonyms **:** CI food yellow 13, INS No. 104.

Chemical name **:** Disodium2-(1,3-dioxo-2-indanyl)-6,8-quinolinesulphates,

disodium2(2quinolyl)-indane-1,3-dionedisulfonates.

Empirical formula **:** $C_{18}H_9NNa_2O_8S_2$

Molecular weight: 477.38

Physical state: Yellow powder or granules

Solubility **:** Soluble in water, sparingly soluble in ethanol.

Melting point **:** 150^{o}C

pH: 8.0-9.0

Stability and storage:

Stable under ordinary conditions. The bulk material should be stored in a well closed container in a cool, dry place.

Applications: It is used in coloring food, cosmetics and medications.

4.4. INNNOVATOR PRODUCT SPECIFICATION

Description:

- Yellow coloured, ovaloid film-coated tablets.

Composition: Clarithromycin 500 mg.

Excipients used:

Croscarmellose sodium, cellulose microcrystalline, silicon dioxide, povidone, stearic acid, magnesium stearate, talc, hypromellose, hydroxypropylcellulose, propylene glycol, sorbitan monooleate, titanium dioxide, sorbic acid, vanillin, quinoline yellow E104.

Physical parameter: The physical dimension is 19.5×9.5mm.

Packaging : It is available in a 300 µ PVC, PVdC Al foil blister pack.

Dose and its administration: Patients with respiratory tract infections and skin or soft tissue infection.

Adults (including the elderly):

- The usual dose is 250 mg twice daily although this may be increased to 500mg twice daily in severe infections. The usual duration of treatment is 6 to 14days.

Children:

- Children older than 12 years: as same as adults.
- The use of clarithromycin 500 mg tablets are not recommended for children younger than 12 years

  Patients with duodenal ulcer and eradication of H.*Pylorii*

- It has both dual and triple therapy. The usual duration of treatment is 6 to 14 days.

Shelf life:36 months

Storage: Store in a cool place, protected from light and moisture.

4.5. LIST OF INSTRUMENTS

Table No. 5: List of instruments

S. No.	Instruments	Manufacturers/suppliers
1	Electronic balance	Adventurer Mettler Toleda.
2	pHMeter	Lab India
3	FTIR spectrophotometer 8300	Shimadzu- corporation, Japan.
4	HPLC with PDA/Quartarnary system	Shimadzu - corporation, Japan.
5	Disintegration tester	Electrolab, ED-2L, India
6	Dissolution apparatus (Disso2000)	Lab India dissolution test apparatus.
7	Friability test apparatus	Electro lab, ET-2, India.
8	Bulk density apparatus	Thermionic, Campbel Electronics.
9	Sonicator	Fast clean.

4.6. LIST OF EQUIPMENTS

Table No. 6: List of equipments

S. No.	Equipments	Manufacturer/supplier
1	Moisture balance	OHAVS moisture balance
2	Vernier caliper	Mitutoyo corps, Japan
3	Hardness tester	Monsanto test apparatus. Tab machines.
4	Stability cum Humidity chamber	Thermolab India
5	Fluidized bed dryer	Pam Glatt
6	8 Station tablet compression Machine	Accura, Ahmedabad

4.6. EXPERIMENTAL METHODS

4.6.1. PREFORMULATION STUDIES [67,68]

Preformulation is usually defined as the science of the physicochemical characterization of candidate drugs. Any studies carried out to define the conditions under which the candidate drug should be formulated can also be termed Preformulation.

The basic purpose of the Preformulation activity is to provide a rational basis for the formulation approaches, to minimize the chances of success in formulating an acceptable product and to ultimately provide a basis for optimizing drug product quality and performance. The first step in any formulation activity is careful consideration of a complete physicochemical profile of the active ingredients available, prior to initiating a formulation development activity.

CONTENTS OF PREFORMULATION STUDIES

- Background – Compound chemical name, chemical structure, solvent of recrystallization, purity, therapeutic category.
- Organoleptic properties – Appearance, color and odor.
- Microscopic examination – Crystal habit, crystal shape and size.
- Physical properties – Density, particle size, surface area, flow properties, hygroscopicity.
- Solution properties – pH of solution, solubility and dissolution rate, drug excipient compatibility study.

A. Evaluation of API

The evaluation of clarithromycin was done according to USP. Following are some of the important parameters evaluated during preformulation studies and results are tabulated in **Table No.22** .

a. DESCRIPTION

It is the initial evaluation during preformulation studies, which assess the color and odor of the substance. This was only a descriptive test.

b. SOLUBILITY

Aqueous solubility is an important physicochemical property of drug substance, which determines its systemic absorption and in turns its therapeutic drug.

Table No 7: Solubility specifications

Descriptive terms	**Approximate volume of solvent in milliliters per gram of solute**
Very soluble	Less than 1
Freely soluble	From 1 to 10

Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble	More than 10,000

c. pH

The pH is the measure of negative logarithm of hydrogen ion concentration of an aqueous solution. It is one of the most important factors from the stand point of solubility, stability and physiological suitability of a formulation. The pH value of a solution is determined potentiometrically by means of a glass electrode.

d. MELTING POINT

The temperature at which the first particle of the substance completely melts is regarded as melting point of the substance. The temperature at which the first particle start to melt and last particle completely melts is regarded as melting range. Melting point of clarithromycin was conducted as per monograph.

e. CHEMICAL NATURE

Solubility, stability, bioavailability etc., of a drug substance depends on its chemical nature and this information helps to design a suitable dosage form.

f. HYGROSCOPICITY: It is defined as the ability of a substance to absorb moisture from the environmental conditions it is exposed.

Table No8 : Interpretation of results based on % increase in moisture

S.No.	NATURE OF SAMPLE	RESULT OF THE DETERMINATION

1	Non hygroscopic	No water absorption at RH less than 90%,after 1 week, water absorption is less than 20% at more than 90%RH.
2	Slightly hygroscopic	No water absorption at RH less than 80%,after 1 week, water absorption is less than 40% at more than 80%RH.
3	Moderately hygroscopic	Water absorption doesn't increase to more than 5% at RH less than 60% after 1 week, water absorption is less than 50% at more than 80%RH
4	Very hygroscopic	Water absorption occurs at RH as low as 40% after 1 week, water absorption is more than 50% at more than 80%RH

g) Particle size determination:

Particle size distribution is an important factor which determines number of parameters like dissolution rate, bioavailability, content uniformity, flow properties, texture and stability of formulation. Number of methods like sieving, microscope, laser diffraction methods etc., can analyze the particle size. The particle size of the clarithromycin was done by sieving method.

Table No 9 : Classification of sample was based on the % of sample retained or passed on test sieves.

S.No.	NATURE OF SAMPLE	RESULT OF DETERMINATION
1	Coarse powder	NLT 95% of the sample mass pass through #14 and NMT 40% pass through #36
2	Moderately coarse powder	NLT 95% of the sample mass pass

		through #25 and NMT 40% pass through #60
3	Moderately fine powder	NLT 95% of the sample mass pass through #36 and NMT 40% pass through #100
4	Fine powder	NLT 95% of the sample mass pass through #100 and NMT 40% pass through #150
5	Very fine powder	NLT 95% of the sample mass pass through #150 and NMT 40% pass through #200
6	Super fine powder	NLT 90% by number of particles are less than 10µm

h. LOSS ON DRYING

LOD was performed according to USP monograph. Dry the raw material at 105º for 2 h. NMT 1.0-1.5 % of its weight must be lost.

A. Drug-excipient compatibility studies

In the tablet dosage form the drug is in intimate contact with one or more excipients; the latter could affect the stability of the drug. Knowledge of drug-excipient interactions is therefore very useful to the formulator in selecting appropriate excipients. This information may be present for known drugs. For new drugs or new excipients, the preformulation scientist must generate the needed information.

- **Physical observation:**

Active ingredient was mixed well with all excipients in binary ratio and small portion of this mixed powder was placed in a 2ml of cleaned and dried vial (USP Type I). This vial was kept for observation in stability chamber at 30°C ± 2°C / 65 ± 5% RH, 40°C ± 2°C / 75 ± 5% RH. Mixtures were also placed at 2°C -8°C, 50°C and room temperature (Control). Physical observation has been carried out visually at the initial stage and after 3 months in 40°C ± 2°C / 75 ± 5% RH and one month in 50°C of exposure to the stated conditions respectively.

Table No.10: Drug – excipient compatibility studies

S.No	Drug and excipients	Ratio
1	Drug + Microcrystalline cellulose PH101	1:1
2	Drug + Microcrystalline cellulose PH102	1:1
3	Drug + Microcrystalline cellulose PH112	1:1
4	Drug + Hydroxy propyl cellulose	5:1
5	Drug + Povidone	5:1
6	Drug + Pregelatinised starch	5:1
7	Drug + Croscarmellose sodium	10:1
8	Drug + Talc	10:1
9	Drug + Aerosil	10:1
10	Drug + Magnesium Stearate	10:1

- **Chemical compatibility studies by FT-IR :**

Physical compatibility studies were assured by FT-IR studies. The crude drug sample, drug-excipient mixtures of the formulation were chosen for the study. The FT-IR spectra's of the above samples were studied after a period of 30 days from preparation of the mixtures,to facilitate prompt detection of incompatibility.The spectra's were obtained by preparing Potassium bromide pellets under dry condition by using pellet press.

The spectra of the crude drug sample and that of the drug-excipient mixtures were compared to check the incompatibility problems. If there are no changes in peaks of mixture when compared to pure drug, it indicates the absence of chemical interaction. The FT-IR spectra's were as shown in **Figure No.4 &5**.

4.6.2. SELECTION OF EXCIPIENTS

Excipients used in the present study were selected according to innovator excipient list. Excipients include Croscarmellose Sodium, Povidone, Pregelatinised starch, Micro Crystalline Cellulose, Magnesium Stearate, Talc, Colloidal silicon dioxide, hydroxyl propyl cellulose in the tablet core. The approximate quantity for each excipient to be used was found using finger print method.

FINGER PRINT METHOD

- ✓ Tablet of innovator product has been taken and dissolved in 100 ml of water. It was stirred continuously or kept aside for about 60 min.
- ✓ Whatman filter paper No. 42 was selected and it was initially placed in desiccator for 10 min, and dried at 105º C for 30 min.
- ✓ Dried filter paper was then weighed and initial weight was noted after cooling in desiccator for 10 min.

- ✓ The tablet dissolved in water was filtered and the filter paper was dried with the un-dissolved particles.
- ✓ Soon after drying, weight of the paper was noted. The amount of water soluble excipients and insoluble excipients can be calculated.

1.6.3. DEVELOPMENT OF PRELIMINARY TRIAL BATCH

From finger print method, approximate quantities have been identified and trial batch has been taken.

PREPARATION OF GRANULES FOR COMPRESSION

Immediate release tablet of clarithromycin was prepared by wet granulation method. All tablet ingredients was accurately weighed as mentioned in **Table No.11**. The average weight of each uncoated tablet was 850 mg.

IV. METHODOLOGY

4.6.3. Formulation of Clarithromycin Immediate-release Tablet

The method used in the formulation of clarithromycin IR tablets was wet granulation non-aqueous method.

All the batch formulations in these studies are formulated by wet granulation method.

1. **Weighing:**
   Accurately weigh specified quantity of raw materials clarithromycin, croscarmellose sodium in a weighing balance.

2. **Sifting:**
   Clarithromycin is sifted through 30#, croscarmellose sodium through 60# and placed in a poly bag. Mix the sifted materials for 5min.

3. **Binder preparation:**
   Dissolve Povidone in Isopropyl alcohol under continuous stirring.

4. **Granulation:**
   Granulate with required quantity of binder solution by kneading method (Hand granulation) or in FBP.

5. **Drying:**
   Dry at an inlet temperature of 60°C and product temperature of 40°C in FBP, until the moisture content of granules is dried.

6. **Sizing:**Using # 20 reduce the size of granules to get the uniform particle size.

7. **Mixing & Lubrication:**
   Croscarmellose sodium, pregelatinized starch and microcrystalline cellulose of required grade are sifted through # 60 and along with dried granules are mixed for 5 minutes.Finally, the above granules are lubricated using specified

quantity of magnesium stearate after sifting it through # 60 and mix for 5 minutes.

8. **Compression:**Compress the above granules using 19.5 × 9.5 mm punches at an average weight of 850 mg.

9. PROCESS FLOW CHART

Dispensing

↓

Sifting

↓

Dry mixing

↓

Wet granulation

↓

Drying

↓

Screening/sizing

↓

Lubrication

↓

Compression

↓

Coating

FORMULATION TRIAL BATCHES

S.No.	Ingredients	F-1 (mg/tab)	F-2 (mg/tab)	F-3 (mg/tab)	F-4 (mg/tab)	F-5 (mg/tab)	F-6 (mg/tab)	F-7 (mg/tab)	F-8 (mg/tab)
1	Clarithromycin	500.00	500.00	500.00	500.00	500.00	500.00	500.00	500.00
2	Croscarmellose sodium	17.00	17.00	17.00	17.00	17.00	17.00	17.00	17.00
4	Povidone	-	-	21.00	34.25	35.00	35.00	35.00	35.00
5	Colloidal silicon dioxide	-	-	-	-	6.00	8.50	8.50	-
6	Hydroxy propyl Cellulose	15.00	20.00	-	-	-	-	-	-
7	Microcrystalline cellulose PH101	235.70	229.30	230.00	220.00	-	-	-	-
8	Croscarmellose sodium	25.50	25.50	-	25.50	25.50	25.50	25.50	25.50
9	Microcrystalline cellulose PH112	-	-	39.45	-	-	-	-	-
10	Microcrystalline cellulose PH102	50.00	48.00	-	36.00	251.50	249.00	199.00	196.00
11	Pregelatinised starch	-	-	-	-	-	-	50.00	50.00
12	Talc	-	-	8.50	4.25	10.0	8.65	8.65	9.50
13	Colloidal silicon dioxide	2.55	3.82	4.30	4.50	-	-	-	9.50
14	Magnesium stearate	4.25	6.38	4.75	8.5	5.00	6.35	6.35	7.50
15	Isopropyl Alcohol	-	-	-	q.s	q.s	q.s	q.s	q.s
16	Purified water	q.s	q.s	q.s	-	-	-	-	-
Average Weight		**850**	**850**	**850**	**850**	**850**	**850**	**850**	**850**

Table No.11: Formulation trial batches

PERCENTAGE OF INGREDIENTS USED IN TRIAL BATCH FORMULATIONS

Trial No. 12: Percentage of Ingredients used in trial batch formulations

S.No.	Ingredients	MATERIAL USED IN PERCENTAGE DURING FORMULATION							
		F-1 (%/tab)	**F-2 (%/tab)**	**F-3 (%/tab)**	**F-4 (%/tab)**	**F-5 (%/tab)**	**F-6 (%/tab)**	**F-7 (%/tab)**	**F-8 (%/tab)**
1.	Clarithromycin	58.82	58.82	58.82	58.82	58.82	58.82	58.82	58.82
2.	Croscarmellose sodium	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
3	Povidone	-	-	2.47	4.029	4.11	4.11	4.11	4.11
4.	Colloidal silicon dioxide	-	-	-	-	0.70	1.00	1.00	-
5	Hydroxy propyl Cellulose	2.35	2.35	-	-	-	-	-	-
6	Microcrystalline cellulose PH101	27.14	26.97	27.058	25.88	-	-	-	-
7	Croscarmellose sodium	3.00	3.00	-	3.00	3.00	3.00	3.00	3.00
8	Microcrystalline cellulose PH112	-	-	4.64	-	-	-	-	-
9	Microcrystalline cellulose PH102	5.88	5.64	-	4.23	29.52	29.29	23.41	23.05
10	Pregelatinised starch	-	-	-	-	-	-	5.88	5.88
11	Talc	-	-	1.00	0.50	1.17	1.01	1.01	1.11
12	Colloidal silicon	0.3	0.44	0.50	0.529	-	-	-	1.11

	dioxide								
13	Magnesium Stearate	0.5	0.75	0.55	1.00	0.588	0.74	0.74	0.88
15	Isopropyl Alcohol	-	-	-	q.s	q.s	q.s	q.s	q.s
16	Purified water	q.s	q.s	q.s	-	-	-	-	-

4.6.4. COATING SOLUTION FORMULA

Clarithromycin tablet was coated using the following ingredients mentioned in the Table No.13.

Table No.13: Coating solution formula

S.No.	Ingredients	Uses	Qty/500 Tablet (gm)
1.	Hydroxy propyl methyl cellulose 15 cps	Film former	7.20
2.	Ethyl cellulose	Coating agent	2.40
3.	Titanium dioxide	Opacifizer	2.20
4.	Talc	Anti caking agent	1.175
5.	Quinoline yellow (lake)	Colour	0.250
6.	Ethyl vanillin	Flavour	1.2
7.	Propylene glycol	Plasticizer	1.65
8.	Dichloro methane	Solvent	144ml
9.	Iso propyl alcohol	Solvent	144ml

PROCEDURE

- Dissolve ethyl cellulose in isopropyl alcohol in a stainless steel vessel and disperse HPMC15 cps to the ethyl cellulose solution.
- Add dichloro methane to ethyl cellulose, HPMC solution and mix well for 10 minutes under mechanical stirring.
- Weigh accurately quinoline yellow lake, titanium dioxide and talc. Pass through sieve No.60 and triturate in a mortar. Transfer to above stirred solution and mix well under stirring.

- Add propylene glycol to the above steps and mix well under stirring.
- Load the tablets in coating pan with baffles fixed and sets the parameters according to the suitability of the machine.

4.6.5. FILM COATING PARAMETERS

Table No.14: Film coating parameters

Specification	Film coated
Coating pan	12”
Atomizing air pressure	3 – 4 kg/cm^2
Inlet air temperature	45 – 50ºC
Outlet air temperature	40 – 45ºC
Bed temperature	30-35ºC
Pre-drying in pan	15 min at 45ºC
Final drying in pan	30 – 45 min at 45ºC
Post drying in pan	30 min air drying
Relative humidity	40 ± 5% RH

4.6.6. OPTIMIZATION OF TRIAL BATCH (F8) BY FULL FACTORIAL DESIGN

In order to obtain “best” or an “optimized product” nine different formulations were generated using a 3^2 randomized full factorial. Based on preformulation study the amounts of croscarmellose sodium (X_1) and microcrystalline cellulose PH102 (X_2) were selected as the independent factors, studied at 3 levels each (-1, 0, +1). The percentage drug release (y_1) and disintegration time (y_2) were taken as dependent factors. Experimental trials were

performed at all 9 possible combinations of X_1 and X_2. Batches for factorial design are shown **in Table No.15**[79,80]

Table No.15: Formulation trials as per experimental design

Trial No.	***Coded factor levels***	
	X_1	***X_2***
I	*-1*	*-1*
II	*-1*	*0*
III	*-1*	*1*
IV	*0*	*-1*
V	*0*	*0*
VI	*0*	*1*
VII	*1*	*-1*
VIII	*1*	*0*
XI	*1*	*1*

Translation Of Coded Levels In Actual Units			
Coded level	*-1*	*0*	*1*
X_1: CCS (%)	*2*	*3*	*4*
X_2:MCC102 (%)	*21*	*23*	*25*

4.6.7. FORMULATION TRIAL BATCHES FOR OPTIMIZED BATCHES

Ingredients	***Formulation Code Qty/Tab (mg)***								
	OF1	***OF2***	***OF3***	***OF4***	***OF5***	***OF6***	***OF7***	***OF8***	***OF9***
Clarithromycin	*500*	*500*	*500*	*500*	*500*	*500*	*500*	*500*	*500*
Croscarmellose sodium	*17.0*	*17.0*	*17.0*	*17.0*	*17.0*	*17.0*	*17.0*	*17.0*	*17.0*
Povidone	*35.00*	*35.00*	*35.00*	*35.00*	*35.00*	*35.00*	*35.00*	*35.00*	*35.00*
Croscarmellose sodium	*25.25*	*25.25*	*25.25*	*25.50*	*25.50*	*25.50*	*25.75*	*25.75*	*25.75*
Microcrystalline cellulose PH102	*194.5*	*196.5*	*198.5*	*194.5*	*196.5*	*198.5*	*194.5*	*196.5*	*198.5*
Pregelatinised starch	*51.75*	*49.75*	*47.75*	*51.5*	*49.5*	*47.50*	*51.25*	*49.25*	*47.25*
Talc	*9.50*	*9.50*	*9.50*	*9.50*	*9.50*	*9.50*	*9.50*	*9.50*	*9.50*
Colloidal silicon Dioxide	*9.50*	*9.50*	*9.50*	*9.50*	*9.50*	*9.50*	*9.50*	*9.50*	*9.50*
Magnesium Stearate	*7.50*	*7.50*	*7.50*	*7.50*	*7.50*	*7.50*	*7.50*	*7.50*	*7.50*
Isopropyl Alcohol	*q.s*	*q.s*	*q.s*	*q.s*	*q.s*	*q.s*	*q.s*	*q.s*	*q.s*
TOTAL	***850***	***850***	***850***	***850***	***850***	***850***	***850***	***850***	***850***

Table No.16: Formula for optimized batches of F8

Formulation procedure was repeated as per above trial batch and coated. All the optimized formulations were evaluated for its description, average weight, friability, thickness, hardness, disintegration time, assay and dissolution.

4.6.8. Evaluation of granules of clarithromycin (Precompression parameters)

It is a very important parameter to be measured because it affects the mass of uniformity of the dose. It is usually predicted from flow property, bulk density, tapped density, compressibility index and hausners ratio. Clarithromycin granules were evaluated by the following method.

Flow Property Measurements

It is very important parameter to be measured since it affects the mass of uniformity of the dose. It is usually predicted from angle of repose, bulk density, tapped density, compressibility index and hausners ratio.

a. Density (g/ml)

Granule density, true density and bulk density may influence compressibility, tablet porosity, flow property, dissolution and other properties. Higher compression load is required in case of dense and hard granules which in turn increase the tablet disintegration and drug dissolution time. Density is usually determined by Pycnometer.

b. Bulk density[70, 71]

Bulk density is the ratio of the weight of the powder to the bulk volume it occupies. It is expressed in g/ml. Weighed quantity of clarithromycin granules was transferred into a 50ml measuring cylinder and the volume occupied by granules was measured. Bulk density was measured using the formula.

$$P_i = M/V_0$$

Where,

P_i - Bulk density

M - Mass of the blend

V_0 - Untapped Volume

c. Tapped density (ρ_t) [70,71]

It is done by two methods according to monograph.

USP TYPE 1 – Fixed drop of 14 ± 2 mm at a nominal rate of 299 drops/min

USP TYPE 2 – Fixed drop of 3 mm ± 10 % at a nominal rate of 250 drops/min

Tapped density is achieved by mechanically tapping a measuring cylinder containing a powder sample. After observing the initial volume, the cylinder is mechanically tapped, and volume readings are taken until little further volume change is observed.

The measuring cylinder containing a weighed quantity of granules (after measurement of bulk density) was subjected to 500 taps in tapped density tester (Electro Lab USP II). The tapped density was calculated by using the formula,

$$\boxed{\rho_t = m / V_i}$$

Where m = mass of the blend

V_i = tapped volume

d. Carr's compressibility index [72,73]

Compressibility is the ability of powder to decrease in volume under pressure. Using untapped density and tapped density the percentage compressibility of granules were determined, which is given as Carr's compressibility index. **Table No: 9** show the percentage compressibility index and its flow characteristics.

$$\mathbf{CI = V_i - V_0 / V_i \times 100}$$

Where,

CI = Compressibility index

V_0 = Bulk density V_i= Tapped density

Table No.17: Compressibility index

Compressibility index (%)	**Flow characters**
< 10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
> 32	Very poor

e. Hausner's Ratio [72,73]

It is the measurement of frictional resistance of the drug. The ideal range should be 1.2 – 1.5, it was determined by the ratio of tapped density and bulk density.

$$\text{Hausner's Ratio} = \frac{V_0}{V_i}$$

Where,

V_i - Untapped density

V_0 - Tapped density

Hausner's Ratio

Table No.18

Flow character	Hausner's ratio
Excellent	1.00 – 1.11
Good	1.12 – 1.18
Fair	1.19 – 1.25
Passable	1.26 – 1.34
Poor	1.35 –1.45
Very Poor	1.46 – 1.59
Very Very Poor	> 1.60

f. Angle of repose [73,74]

Angle of Repose (θ) is the maximum angle between the surface of a pile of powder and horizontal plane. It is usually determined by fixed funnel method and is the measure of the flow ability of powder/granules**. Table No: 19** shows the flow properties and corresponding angle of repose.

Procedure

Weighed quantity of granules was passed through a funnel kept at a height of 2 cm for the base. The powder is passed till it forms heap and touches the tip of the funnel. The radius was measured and angle of repose was calculated by using the formula.

$$\theta = \tan^{-1}(h/r)$$

Where,

θ = Angle of repose

h = height of the heap of pile, r = radius of the base of pile

Table No.19: Flow properties and corresponding angle of repose

Flow properties	**Angle of repose (^{o})**
Excellent	25-30
Good	31-35
Fair – aid	36-40
Passable	41-45
Poor	46-55
Very poor	56-65
Very very poor	>66

g. Moisture content:

Initially 5g of weighed granules were taken and kept for drying at 105ºC for a required time in an oven. Then removed and again reweighed and noted the final weight. The difference in weight was noted as moisture content.

$$\textbf{Moisture content} = \frac{\textbf{Initial weight – Final weight}}{\textbf{Initial weight}} \times \textbf{100}$$

4.6.9. Evaluation of tablets [23,24,25,26,27,74,75]

I) Post compression parameters

The formulated film coated tablets were evaluated for the following physicochemical parameters,

a. Thickness:

Thickness mainly depends on die filling, physical properties of material to be compressed under compressional force. There is bound to be a small variation in the thickness of individual tablet in a batch. But it should not be apparent to the unaided eye. The thickness and diameter were measured by using vernier calipers.[75]

b. Hardness:

Tablet requires certain amount of strength or hardness, measured by Monsanto hardness tester. Ten tablets were randomly picked from each formulation and evaluated for hardness during manufacturing and are expressed in kg/cm^2.[75]

c. Friability:

Friability was performed by using friability test apparatus, normally pre-weighed ten tablets were placed in the plastic chamber of friabilator. This was then operated for 100 revolutions. Tablets were dropping from a distance of six inches with each revolution. Tablets are then dusted and reweighed. Loss of less than 1% in weight is considered to be acceptable. [76]

Ir

$$F(\%) = \frac{\text{Final wt.}}{\text{Initial wt.}} \times 100$$

d. Weight variation test:

Twenty tablets were selected randomly and weighed individually. Calculate average weight and compare the individual tablet weight to the average. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in **Table No.: 20** and none deviates by more than twice the percentage.

Table No.20: Percentage deviation for weight variation test

Average weight of Tablets (mg)	Max. Percentage deviation (%)
130 or less	± 10
More than 130 - Less than 324	± 7.5
324 or more	±5

II) In-vitro dissolution studies: [77,78]

Dissolution for clarithromycin:

Dissolution system:

Apparatus : Dissolution Apparatus USP Type – II (Paddle)

Speed : 50 RPM

Medium : 900 ml of Acetate buffer pH 5.0

Temperature : 37°C ± 0.5°C

Time : 30 Minutes

Procedure :

Preparation of Buffer solution:

13.61 gm of Sodium acetate trihydrate was dissolved in 1L of purified water in 1L volumetric flask and mix. Then Adjust with 0.1M acetic acid to apHof 5.0

Preparation of Standard solution*:*

62.50 mg of clarithromycin USP working Standard was accurately weighed and transferred in a 100ml volumetric flask and dissolved using methanol, and made up to the volume using dissolution medium.

From the above solution, 10 ml was taken in a 50 ml volumetric flask and made up to a volume with mobile phase.

Preparation of sample solution:

Apparatus was set as per above conditions, one tablet placed in each of the six dissolution vessels and started the dissolution test. After completion of 30 minutes, 20 ml of the solution was withdrawn from dissolution bowl. The filtrate was collected after discarding first few ml of the filtrate**.** From this 5 ml of the filtrate was diluted to 25 ml with mobile phase.

Chromatographic system:

Apparatus : HPLC

Column : A stainless steel column (250×4.6mm) packed with Octa decyl silane (C18) bonded to porous silica.

Flow rate : 1.0 ml/min

Column oven temperature : 50^{o}C

Injection volume : 50µL

Wave length : 210 nm

Preparation of buffer solution:

9.113 gm of monobasic potassium phosphate was accurately weighed and dissolved in 1000 ml of water and its pHwas adjusted to 4.0 with dilute ortho phosphoric acid.

Preparation of mobile phase:

Take 650 ml from the above buffer solution and 350 ml of methanol was mixed well, and filtered and degassed.

Procedure:

50 microlitres of filtered portion of the standard solution and sample solution were separately injected into the HPLC system. The chromatogram was recorded and the responses were measured for the major peaks. The amount of drug release of clarithromycin USP was calculated in percentage with respect to label claim by using the following expression.

Calculation forclarithromycin:

$$= \frac{AT}{AS} \times \frac{WS}{100} \times \frac{10}{50} \times \frac{900}{1} \times \frac{25}{5} \times \frac{P}{100}$$

= ——————— mg of clarithromycin released.

$$\% \text{ of drug released} = \frac{\text{mg of drug released} \times 100}{LA}$$

Where,

AT = Area of the clarithromycin in sample solution

AS = Average area of the clarithromycin peak for standard solution

WS = Weight taken in mg for standard solution

P = Percent purity of clarithromycin on as such basis

LA = Labeled amount.

System suitability:

1. % RSD of five replicate injections peak should not be more than 2.0%
2. The theoretical plate for clarithromycin peaks should not be less than 750.
3. The tailing factor for clarithromycin peaks should not be more than 2.0

III) ASSAY (BY HPLC)

Preparation of buffer solution:

9.113 gm of monobasic potassium phosphate was accurately weighed and dissolved in 1000 ml of water and its pH was adjusted to 4.0 with dilute ortho phosphoric acid.

Preparation of mobile phase:

650 ml of the above buffer solution and 350 ml of methanol was mixed well, filtered and degassed.

Preparation of standard stock solution:

62.50 mg of clarithromycin USP working Standard was accurately weighed and transferred in a 100ml volumetric flask and dissolved using methanol, and made up to the volume using mobile phase.

Preparation of standard solution:

10 ml of standard stock solution was taken in a 50ml volumetric flask and made up to a volume with mobile phase. This solution contains about 125µg of clarithromycin per ml.

Preparation of resolution solution:

62.5 mg of clarithromycin USP related compound A was weighed in a 50ml volumetric flask and dissolved using methanol. Then 10 ml of this solution and 10 ml of standard stock solution was transferred to a 50 ml volumetric flask and made up to the volume with mobile phase.

Preparation of sample solution:

20 tablets were weighed and crushed to a fine powder, then weighed 438.0 mg of tablet powder (i.e., equivalent to about 250 mg of clarithromycin) was transferred to 200 ml volumetric flask, then about 75 ml of methanol was added and sonicated for 30 minutes. Diluted with methanol to volume and mixed well, and allowed the solution to settle insoluble matter. Then transferred 5ml of supernatant solution to a 50 ml volumetric flask and made up to volume with mobile phase and mixed well. Passed the solution through filter paper and used this solution as assay preparation.

Chromatographicconditions

Column : A stainless steel column (250×4.6mm) packed with Octa decyl silane (C18) bonded to porous silica.

Flow rate : 1.0 ml/min

Column oven temperature : 50^{o}C

Injection volume : 50µL

Wave length : 210 nm

Procedure:

50 microlitres of filtered portion of the resolution solution, standard solution and sample solution were separately injected into the HPLC system. The chromatogram was recorded and the responses were measured for the major peaks. The content of per tablet was calculated using the following expression.

Calculation:

$$= \frac{AT}{AS} \times \frac{WS}{100} \times \frac{10}{50} \times \frac{200}{WT} \times \frac{5}{50} \times \frac{P}{100} \times \text{Avg.wt} \times 100$$

= ———— mg of clarithromycin per tablet.

Where,

AS = Average area of the clarithromycin peak in standard solution,

sAT = Area of the clarithromycin peak in sample solution,

WS = Weight of clarithromycin taken for standard in g,

WT = Weight of clarithromycin taken for sample in g,

P = Percent purity of clarithromycin on as such basis.

System suitability:

1. % RSD of five replicate injections peak should not be more than 2.0%
2. The theoretical plate for clarithromycin peaks should not be less than 750.
3. The tailing factor for clarithromycin peaks should NLT 0.9 and NMT 1.5.
4. The resolution between clarithromycin and clarithromycin related compound A should not be less than 2.

4.6.10. SIMILARITY FACTOR [81,82,83]

In recent years, FDA has placed more emphasis on a dissolution profile comparison in the area of post-approval changes and biowaivers. Under appropriate test conditions, a dissolution profile can characterize the product more precisely than a single point dissolution test. A dissolution profile comparison between pre-change and post-change products for SUPAC related changes, or with different strengths, helps assure similarity in product performance and signals bioinequivalence.

Among several methods investigated for dissolution profile comparison, f_2 is the simplest. Moore and Flanner proposed a model independent mathematical approach to compare the dissolution profile using two factors, f_1 and f_2.

The difference factor (f_1) calculates the percentage difference between the two curves at each time point and is a measurement of the relative error between the two curves:

$$f_1 = \{[\Sigma_{t=1}^{n} | R_t - T_t |] / [\Sigma_{t=1}^{n} R_t]\} .100$$

where, n is the number of time points, R_t is the dissolution value of the reference batch at time t and T_t is the dissolution value of the test batch at time t.

The FDA and EMEA defined similarity factor as a "logarithmic reciprocal square root transformation of one plus the mean squared (the average sum of squares) differences of drug percent dissolved between the test and the reference products"

In other words, the similarity factor (f_2) is a logarithmic transformation of the sum-squared error of differences between the test T_t and reference products $R_t$over all time points. It represents closeness of two comparative formulations. Generally similarity factor in the range of 50-100 is acceptable according to US FDA.

$$f_2 = 50.\log\{[1 + (1/n)\Sigma_{t=1}^{n}(R_t-T_t)^2]^{-0.5}.100\}$$

General procedure:

i. Determine the dissolution profile (5 units each) of the test and reference products.
ii. Using the mean dissolution values from both the curves at each time interval, calculate the difference factor (f_1) and similarity factor (f_2) using the above equations.
iii. For curves to be considered similar, f_1 values should be close to 0, and f_2 values should be close to 100. Generally, f_1 values up to 15 (0-15) and f_2 values greater than 50 (50-100) ensures sameness or equivalence of the two curves.

The comparative dissolution study was performed to determine the similarity of dissolution profiles for the immediate release clarithromycin (OF7) between the innovator product.The results are tabulated in **Table No. 34.**

If there is more than 85% drug release at 15 mins after dissolution, the FDA guidelines provides that the comparative dissolution study can be surpassed. Hence the study is not performed for the immediate release layer as there is >85% drug release at 15 min.

4.6.11. STABILITY STUDIES[28]

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutics and toxicological specifications. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, and to establish a retest for the drug substance or a shelf life for the drug product and recommended storage conditions. The ICH guideline recommends the following storage conditions for stability studies:

Table No.21: Stability conditions according to ICH guidelines

S. No.	Study	Storage Condition
1.	Long term	25°C±2°C / 60%RH±5%RH
2.	Intermediate	30°C±2°C / 65%RH±5%RH
3.	Accelerated	40°C±2°C / 75%RH±5%RH

As per ICH guidelines, the samples for stability analysis must be exposed to an environment of 40˚C±2˚C / 75%RH±5% RH for a period of 6 months. As per the standard protocol the samples must be analyzed at 0, 1, 2, 3 and 6 months time points.

Accelerated stability studies were performed for the final tablets. As per ICH guidelines, tablets were packed in Alu-Alu blister and required blisters were

placed into the stability chamber. The samples were analyzed at 0, 1, 2 and 3 months time points.

Test Performed

- Physical parameters (Description, Hardness, Thickness, Friability, DT).
- Physiochemical parameter (In-vitro Dissolution Study)
- Chemical parameter (Assay)

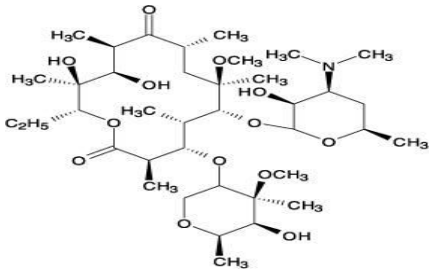
The results of the stability studies are tabulated in Table Nos. 35, 36 and 38. The data was analyzed for any significant change in the values from the initial data.

V. RESULTS AND DISCUSSIONS

5.1. PREFORMULATION STUDIES

a. Evaluation of API

Table No.22: Raw material analysis

S. No	Test	Observation	
1.	Description	White to off-white crystalline powder	
2.	Chemical nature	Chemical structure	
		Molecular formula	$C_{38}H_{69}NO_{13}$
		Molecular weight	748.95
		IUPAC name	6-O-Methyl erythromycin A
3.	Loss on drying	NMT 1.0-1.5%	
4.	Solubility	Practically insoluble in water, Soluble in acetone, Slightly soluble in methanol, ethanol and acetonitrile.	
5.	Particle size of Distribution	Moderately coarse powder	
6.	Hygroscopicity	Non-hygroscopic.	
7.	Melting point	217-220^{o}C	

8.	pH (1%)	8-9

b. Drug-Excipient compatibility studies (Physical observation)

Table No. 23: Compatibility studies of Clarithromycin with excipients.

The preformulation studies of the excipients were mixed with the drug and kept in different conditions, the observed results are as follows:

S.No	Drug+Excipient	Parameter	Initial Value of Parameter	Condition				Comments
				1st Month		3rd Month		
				50° C	2-8°C	RT	40°C	
1	Clarithromycin	Color change	No color change	No color change				Compatible
2	Microcrystalline Cellulose PH101	Colorchange	No color change	No color change				Compatible
3	Cross caramellose Sodium	Color change	No color Change	No color change				Compatible
4	Povidone	Color change	No color Change	No color change				Compatible
5	Hydroxy Propyl Cellulose	Color change	No color Change	No color change				Compatible
6	MCC PH112	Color change	No color Change	No color change				Compatible
7	Pregelatinised starch	Color change	No color Change	No color change				Compatible
8	Talc	Color change	No color Change	No color change				Compatible
9	Aerosil	Color change	No color Change	No color change				Compatible
10	Magnesium Stearate	Color change	No color Change	No color change				Compatible

i) **FT-IR studies:** The FT-IR spectra of the crude drug samples and the drug-excipient mixtures are as shown below.

Figure No. 4: FT-IR spectra of clarithromycin USP- Raw material.

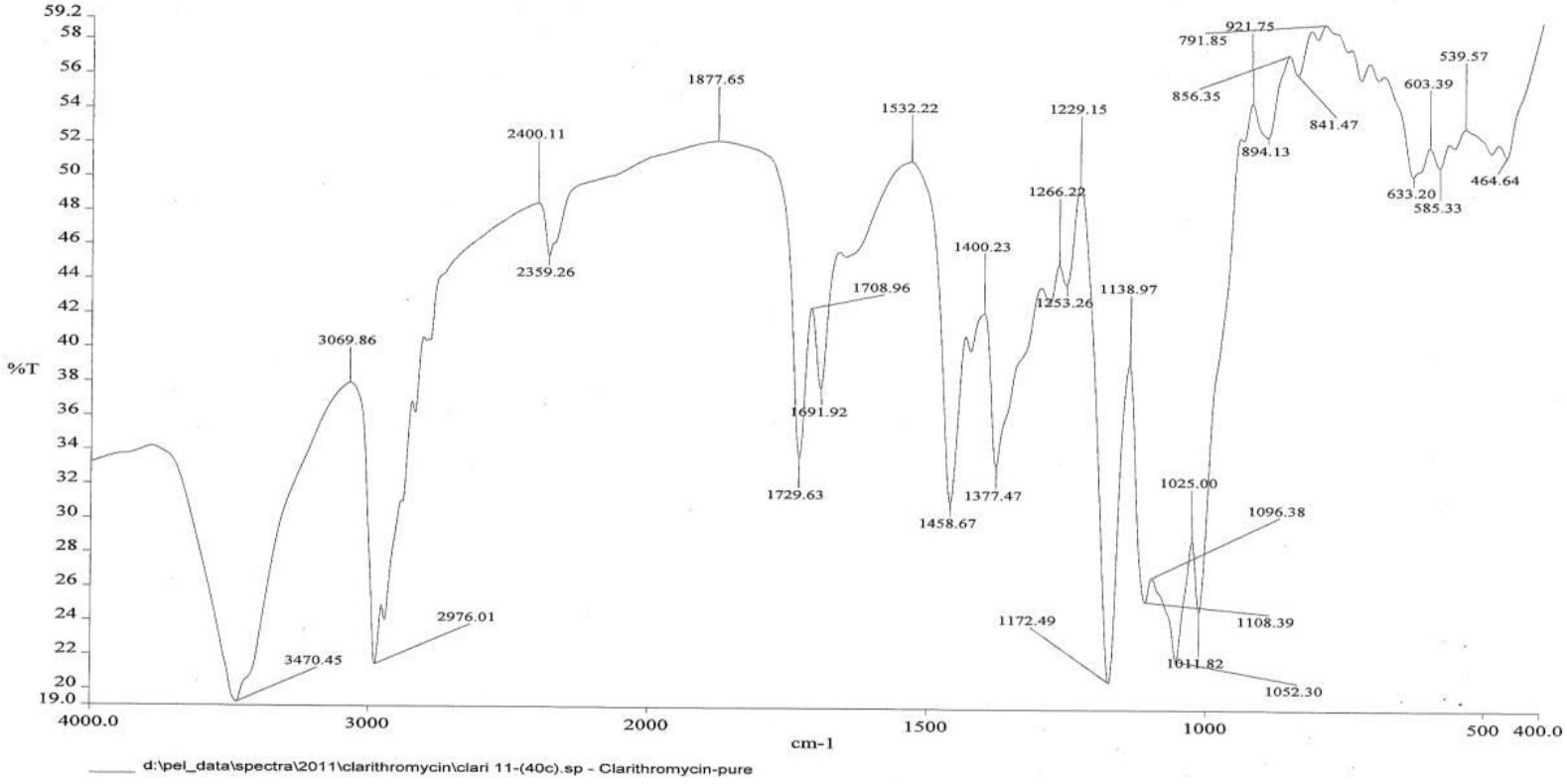

59.2
58
56
54
52
50
48
46
44
42
40
38
36
34
32
30
28
26
24
22
20
19.0
%T
4000.0
3000
2000
1500
1000
500
400.0
cm-1
3069.86
2400.11
2359.26
1877.65
1691.92
1729.63
1708.96
1532.22
1458.67
1400.23
1377.47
1266.22
1253.26
1229.15
1138.97
1172.49
1025.00
1096.38
1108.39
1011.82
1052.30
921.75
791.85
856.35
894.13
841.47
603.39
539.57
633.20
585.33
464.64
3470.45
2976.01
d:\pel_data\spectra\2011\clarithromycin\clari 11-(40c).sp - Clarithromycin-pure

Figure No. 5: FT-IR spectra of clarithromycin and its excipients.

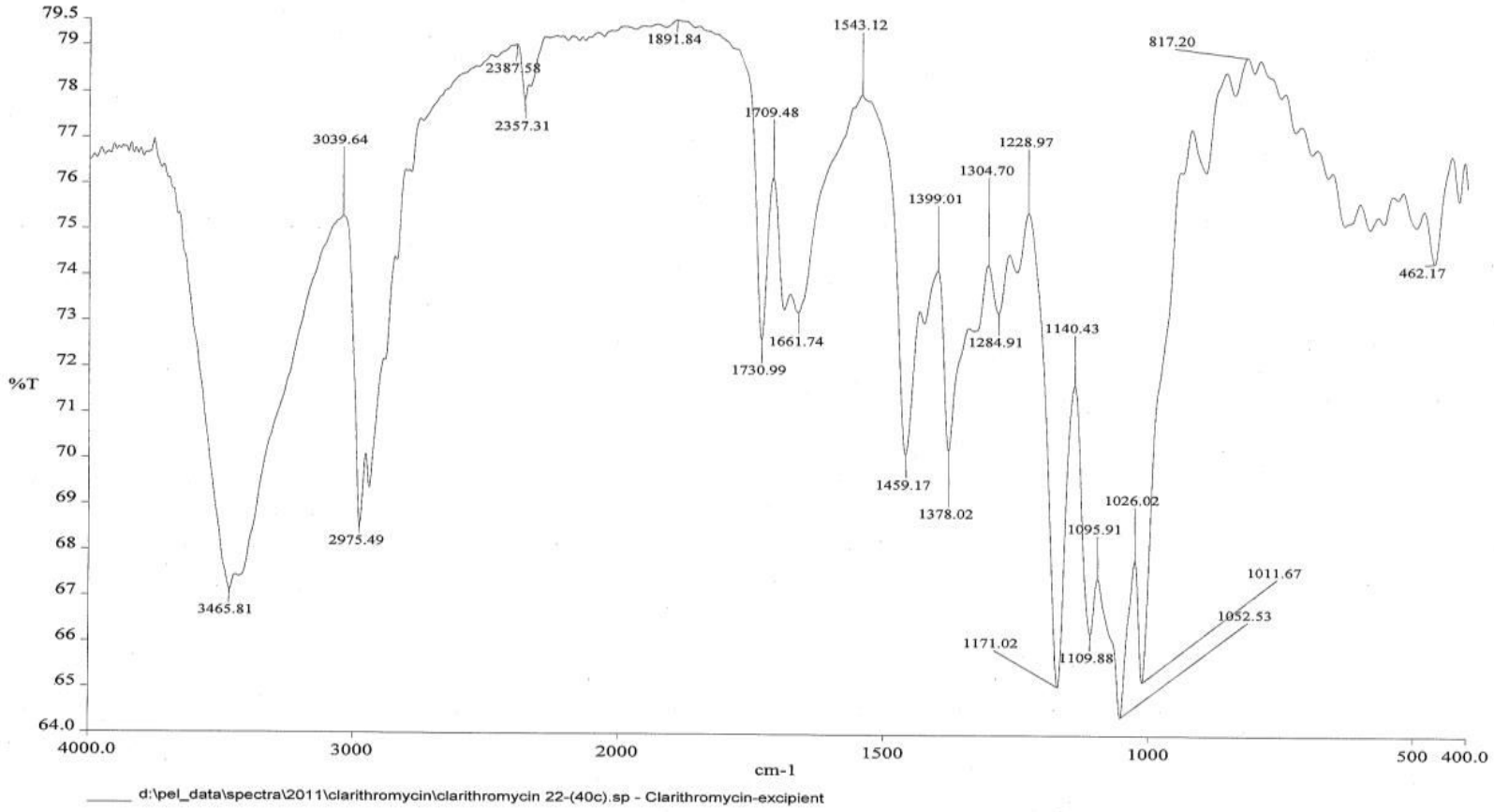


Table No. 24: FTIR spectrum of clarithromycin USP- raw material

Wave Number (cm^{-1})	**Functional Group**
3470 cm^{-1}	OH stretching
2976 cm^{-1}	CH aliphatic
1729 cm^{-1}	C=O stretching
1458 cm^{-1}	CH_3 bending
1266 cm^{-1}	CH_2 bending
1096 cm^{-1}	C—N stretching
1052 cm^{-1}	C—O stretching

Table No. 25: FTIR spectrum of clarithromycin + excipients

Wave Number (cm^{-1})	**Functional Group**
3465 cm^{-1}	OH stretching
2975 cm^{-1}	CH aliphatic
1730 cm^{-1}	C=O stretching
1459 cm^{-1}	CH_3 bending
1228 cm^{-1}	CH_2 bending
1026 cm^{-1}	C—N stretching
1011 cm^{-1}	C—O stretching

Inference: Pure Clarithromycin spectra showed sharp characteristic peaks at 3470, 2976, 1729, 1458, 1266, 1096, 1011 cm^{-1}. These peaks are also prominent in the FTIR spectra's of the physical mixtures containing clarithromycin and other excipients in the final formula. This indicates that there is no interaction between the drug and excipients from both physical observation and FT-IR studies.

5.2. FINGER PRINT METHOD

Weight of tablet taken, a = 922mg

Weight of empty filter paper, b = 1.1966 mg

Weight of empty filter paper after drying, c = 1.1903 mg

Weight of insoluble portion after dried, d = 780 mg

Weight of soluble portion, e = (a-d) = 142 mg

Weight of insoluble portion apart from drug (wt. of core tablet – label claim) = 780-500

=280 mg.

INFERENCE

From the above results and nature of the excipient solubility, trial formula has been developed and formulated.

5.3. EVALUATION OF PRECOMPRESSION PARAMETERS

A. Evaluation of clarithromycin granules: The prepared clarithromycin granules were evaluated for the following parameters, which includes Bulk density, Tapped density, Compressibity Index, Hausner's ratio and Angle of repose.

a) For clarithromycin trial batches

Table No.26: Pre compression parameters for clarithromycin trial batch

S.No	Formulation Code	Bulk density (gm/cc)	Tapped density (gm/cc)	Carr's index (%)	Hausner's ratio	Angle of repose (^{o})	Moisture content (%)
1	F1	0.472±0.0015	0.556±0.012	15.10±0.95	1.17±0.18	33.30±0.60	1.26±0.02
2	F2	0.484±0.0005	0.574±0.047	15.67±0.61	1.18±0.017	34.93±0.68	1.05±0.05
3	F3	0.510±0.0015	0.575±0.010	11.30±0.11	1.12±0.037	33.73±0.27	0.93±0.03
4	F4	0.532±0.0015	0.611±0.013	12.92±0.41	1.14±0.02	33.40±0.73	0.85±0.01
5	F5	0.486±0.001	0.563±0.013	13.67±0.02	1.15±0.02	31.43±0.51	0.83±0.02
6	F6	0.534±0.012	0.593±0.012	9.94±0.01	1.11±0.02	31.7±0.34	0.78±0.03
7	F7	0.522±0.025	0.589±0.02	11.37±0.05	1.12±0.03	30.14±0.29	0.86±0.01

8	F8	0.532±0.013	0.595±0.013	10.58±0.02	1.11±0.01	30.91±0.013	0.84±0.01

*All the values are expressed as mean±SD, n=3.

Inference: The values of compressibility index, Hausner's ratio and angle of repose of all the batches indicate a good flow property of the granules.

B. For optimized batches (Uncoated tablets)

Table No.27: Precompression parameters for optimized batch

S.No.	**Formulation Code**	**Bulk Density *(g/cc)**	**Tapped Density *(g/cc)**	**Compressibility Index (%)***	**Hausner's Ratio***	**Angle of Repose*** (º)**	**Moisture content (%)**
1.	OF1	0.483±0.0015	0.568±0.011	14.96±0.01	1.17±0.01	30.10±0.60	0.85±0.01
2.	OF2	0.487±0.0005	0.554±0.007	12.09±0.05	1.13±0.04	32.43±0.68	0.88±0.03
3.	OF3	0.510±0.0015	0.585±0.015	12.82±0.10	1.14±0.02	32.33±0.27	0.82±0.05
4.	OF4	0.532±0.0015	0.610±0.035	14.66±0.02	1.14±0.01	31.40±0.73	0.77±0.01
5.	OF5	0.532±0.001	0.595±0.013	10.58±0.02	1.11±0.01	30.44±0.51	0.83±0.05

6.	OF6	0.534±0.012	0.603±0.011	11.44±0.03	1.12±0.10	30.33±.34	0.88±0.05
7.	OF7	0.577±0.025	0.647±0.062	12.17±0.02	1.12±0.08	34.54±0.29	0.87±0.05
8.	OF8	0.575±0.013	0.662±0.023	13.14±0.01	1.15±0.06	33.61±0.15	0.79±0.02
9.	OF9	0.576±0.014	0.656±0.016	12.19±0.01	1.13±0.03	32.51±0.11	0.86±0.01

* All the values are expressed asmean ± SD (n=3).

Inference: The values of compressibility index, Hausner's ratio and angle of repose of all the batches indicate an good flow property of granules.

5.3. EVALUATION FOR POST COMPRESSION PARAMETERS

a) Post compression parameters for clarithromycin trial (F1-F8) batch for uncoated tablets.

Table No. 28: Post compression parameters for clarithromycin trial batch uncoated tablets

Formulation code	Average Weight(mg)	Thickness (mm)*	Hardness (kg/cm^2)*	Disintegration(min)	Friability (%)	Weight variation (mg)	Assay (%)
F1	851	6.00 ±0.02	9.3±0.67	1.50±0.02	-	850.0±0.06	-
F2	849	5.98±0.03	9.5±0.35	1.43±0.01	-	849.9±0.74	-
F3	853	5.96±0.08	10.0±0.61	1.54±0.02	-	849.73±0.71	-
F4	854	5.98±0.12	10.0±0.5	1.40±0.01	0.2±0.01	850.16±1.19	101.12
F5	851	6.01±0.05	9.5±0.5	1.22±0.02	0.1±0.01	850.93±1.06	100.34
F6	848	6.04±0.187	9.5±0.35	1.26±0.029	0.32±0.02	849.59±1.18	99.01
F7	849	6.06±0.202	9.5±0.612	1.26±0.049	0.27±0.01	850.3±1.47	103.23
F8	852	6.01±0.11	9.5±0.35	1.28±0.02	0.15±0.02	851.03±0.99	104.67

b) Evaluation of clarithromycin coated tablets of trial batch

Table No. 29: post compression parameters for coated tablets

S.No.	Formulation code	Average Weight (mg)	Thickness (mm)*	Disintegration (min)	Weight variation (mg)	Assay (%)
1	F4	874	6.16±0.031	2.24±0.019	874.18±1.59	98.87
2	F5	877	6.11±0.053	2.25±0.029	876.93±1.46	98.79
3	F6	877	6.17±0.064	2.25±0.02	876.09±1.35	103.28
4	F7	876	6.13±0.039	2.27±0.057	875.93±1.67	102.76
5	F8	874	6.14±0.037	2.25±0.046	877.03±0.99	104.54

* All the values are expressed asmean ± SD (n=6).

Inference: The values of both uncoated and coated parameters in above all batches are in limits.

c) For optimized batches (coated tablets)

Table No. 30: Post compression parameters for optimized batches.

S.No.	Formulation Code	Average Weight (mg)*	Thickness (mm)*	Weight variation test* (mg)	Disintegration test* (min)	Assay# (%)
1.	OF1	875.54	6.12±0.026	876.10±0.94	3.12±0.04	100.04±0.07
2.	OF2	876.27	6.17±0.031	876.56±1.44	3.06±0.06	99.99±0.01
3.	OF3	875.08	6.13±0.025	876.03±1.23	3.27±0.05	102.99±0.01
4.	OF4	874.79	6.19±0.065	874.75±1.35	2.53±0.023	101.99±0.01
5.	OF5	877.02	6.16±0.031	875.03±0.08	2.25±0.018	104.54±0.02
6.	OF6	877.32	6.11±0.053	874.0±1.12	2.24±0.01	103.30±0.63
7.	OF7	876.15	6.17±0.064	876.06±1.05	2.16±0.02	101.69±0.01
8.	OF8	874.14	6.13±0.039	875.89±1.08	2.08±0.04	103.01±0.04
9.	OF9	876.21	6.14±0.037	876.55±0.64	1.55±0.05	103.68±0.01

All the values are expressed as* Mean ± SD (n=6); # Mean ± SD (n=3).

Inference: The values of optimized coated tablet parameters in above all batches are in limits.

5.4. INNOVATOR PRODUCT SPECIFICATIONS

Table No.31: Evaluation specifications for Innovator product

TEST PARAMETERS	**RESULTS**	
Description	Oval shaped, yellow coloured tablet	
Hardness	9-10 (kg/cm^2)	
Thickness	6.0-6.3 mm	
Assay of Clarithromycin by HPLC (% label claim)	99.34 % (NLT 75% to NMT 105%)	
Percentage drug release of Clarithromycin IR tablets	**Time (in min)**	**Percentage drug release**
	5	80.88
	10	95.46
	15	97.55
	20	99.34
	30	102.56

5.6. COMPARATIVE DISSOLUTION PROFILE STUDIES

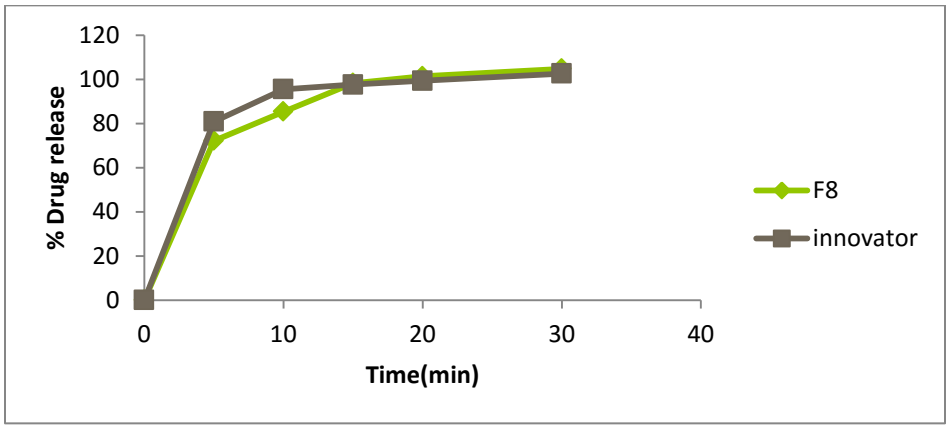
a) Comparative dissolution profile study of clarithromycin coated tablets with innovator product

Table No. 32: Comparative dissolution profile study of clarithromycin coated tablets with innovator product

S.No.	Formulation Code	Cumulative percentage Drug release (min)*				
		5th min	10th Min	15th min	20th min	30th min
1.	F4	68.55±0.12	81.57±0.72	91.23±0.85	92.67±0.23	96.34±0.12
2.	F5	68.84±0.45	84.32±0.75	91.75±0.12	93.62±0.83	98.38±0.34
3.	F6	71.04±0.64	80.56±0.53	91.89±0.64	95.33±0.87	99.47±0.46
4.	F7	69.38±0.87	82.74±0.65	93.40±0.25	96.65±0.37	102.11±0.47
5.	F8	69.19±0.16	85.31±0.25	96.27±0.76	98.36±0.65	101.15±0.72
6.	Innovator	80.88±0.04	95.46±0.14	97.55±0.41	99.34±0.23	102.56±0.34

All the values are expressed as * Mean SD (n=6).

Figure No. 6: Comparative dissolution profile study of clarithromycin coated tablet (F8) with innovator product



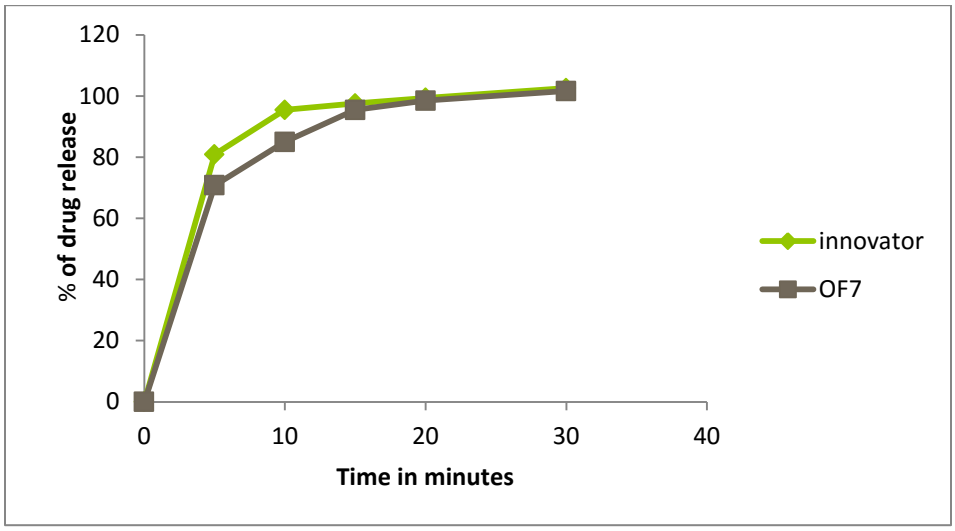
b) Comparative dissolution profile study of clarithromycin optimized coated tablets with innovator product

TableNo. 33: Comparative dissolution profile study of clarithromycin optimized coated tablets with innovator product.

S.No.	Formulation Code	Cumulative percentage Drug release(min)*				
		5th min	10th min	15th min	20th min	30th min
1.	OF1	70.28±0.62	83.61±0.65	95.91±0.96	97.56±0.21	99.38±0.23
2.	OF2	69.04±0.613	83.19±0.64	94.67±0.64	96.73±0.36	98.21±0.56
3.	OF3	68.65±0.649	82.59±0.63	94.76±0.54	96.91±0.15	98.57±0.18
4.	OF4	70.59±0.651	84.68±0.54	95.03±0.48	98.21±0.65	100.46±0.35
5.	OF5	69.19±0.16	83.31±0.25	95.27±0.76	97.36±0.65	101.15±0.27
6.	OF6	68.59±0.621	82.11±0.46	94.98±0.56	96.02±0.64	99.83±0.74
7.	OF7	70.83±0.354	84.96±0.57	95.45±0.54	98.46±0.66	101.62±0.48
8.	OF8	69.54±0.633	83.63±0.56	94.86±0.64	96.08±0.67	100.28±0.13
9.	OF9	68.73±0.458	82.77±0.68	93.88±0.26	96.46±0.64	101.14±0.25
10.	Innovator	80.88±0.04	95.46±0.14	97.55±0.41	99.34±0.23	102.56±0.34

All the values are expressed as* Mean SD (n=6).

Figure No.7: Comparative dissolution profile study of clarithromycin optimized coated tablet (OF7) with innovator product



Inference: Dissolution profile of optimized coated tablets found to be similar with all above batches and innovator drug dissolution profile. Among the entire optimized batches, formulation OF7 has been selected for calculating similarity factor, since it shows faster disintegration time and rapid drug release. Similarity factor was calculated by comparing the in-vitro drug release profile for batch OF7 with the innovator product.

5.7. COMPARITIVE DISSOLUTION PROFILE

This comparative dissolution study performed between the formulation OF7 and the innovator product. The formulation OF7 has been selected for comparative dissolution study, since it shows faster disintegration time and rapid drug release compared to all optimized tablets.

Table No. 34: Comparative dissolution profile for OF7 and innovator product.

S.No.	Dissolution time points	Formulation OF7*	Innovator product*	OF7	
				Dissimilarity factors (f1) 0-15	Similarity factor (f2) 50-100
1.	5^{th} min	70.83	80.88	5.147	59.658
2.	10^{th} min	84.96	95.46		
3.	15^{th} min	95.45	97.55		
4.	20^{th} min	98.46	99.34		
5.	30^{th} min	101.62	102.56		

*** Mean ± SD (n=6)**

Inference: The comparative dissolution profile of similarity and dissimilarity profile was studied for formula OF7 and innovator product. The satisfactory resultwas observed.

5.8. STABILITY STUDIES

Accelerated stability studies were carried out for the OF7 batch. As per ICH guidelines, the stability study data are listed below.

a) Stability study data for batch –OF7 (Post compression parameters)

Table No. 35: Stability studies for post compression parameters of OF7

Post compression Parameters	**Storage condition 40˚C ± 2˚C / 75% RH ± 5% RH**			
	Initial	**1st month**	**2nd month**	**3rd month**
Description	*	*	*	*
Average weight (mg)	875.0±0.85	875.0±0.96	876.0±0.05	876.15±0.02
Hardness(Kg/cm^2)	10.0±0.09	9.5±0.77	9.5±0.44	9.5±0.09
Thickness(mm)	6.17±0.037	6.17±0.12	6.16±0.34	6.16±0.02
Disintegration time (sec)	2.16±0.046	2.20±0.06	2.14±0.08	2.06±0.05

* yellow coloured film-coated tablet.

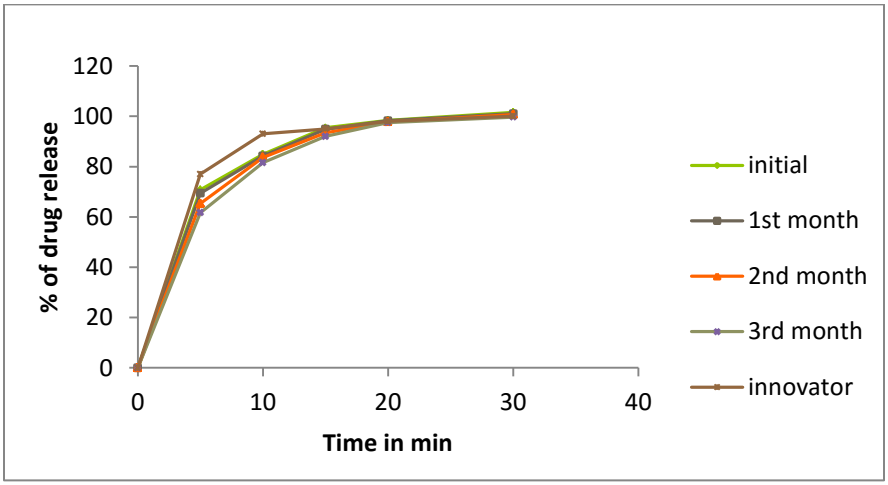
Inference: The accelerated stability study results were found to be satisfactory and within limits.

b) In vitro dissolution study –OF7, stability batch

Table No. 36: Stability studies of invitro dissolution profile for OF7

Dissolution Time points (min)	**Storage condition 40˚C ± 2˚C / 75% RH ± 5% RH**				
	Initial	**1st month**	**2nd month**	**3rd month**	**Innovator**
5	70.83±0.354	69.45±0.21	65.27±0.70	61.66±0.28	77.34±0.18
10	84.96±0.57	84.23±0.54	83.65±0.69	81.57±0.42	93.67±0.22
15	95.45±0.54	94.89±0.16	93.45±0.21	92.03±0.27	95.27±0.76
20	98.46±0.66	98.24±0.02	97.82±0.25	97.56±0.92	98.87±0.01
30	101.62±0.48	101.03±0.06	100.67±0.62	99.73±0.12	100.56±0.05

Figure No. 8: In vitro dissolution study –OF7, stability batch



Inference: There are no significant changes in the physical parameters and analyzed characteristics of the tablets are observed during the period of study. The drug invitro dissolution profile also remained within the limits, at the end of 3rd month of 40˚C ± 2˚C / 75% RH ± 5% RH . From this stability studies, it is concluded that the formulated tablets are stable.

c) Assay – OF7, stability batch

Table No. 37: Stability studies for assay of OF7.

Assay (%)	**Storage condition 40˚C ± 2˚C / 75% RH ± 5% RH**			
	Initial	**1st month**	**2nd month**	**3rd month**
OF7	101.69	100.27	99.74	96.88
Innovator	99.34	98.70	97.62	96.47

Figure No. 9: Assay – OF7, stability batch

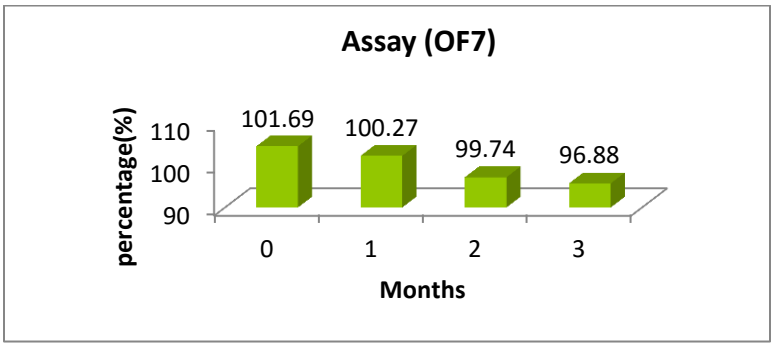
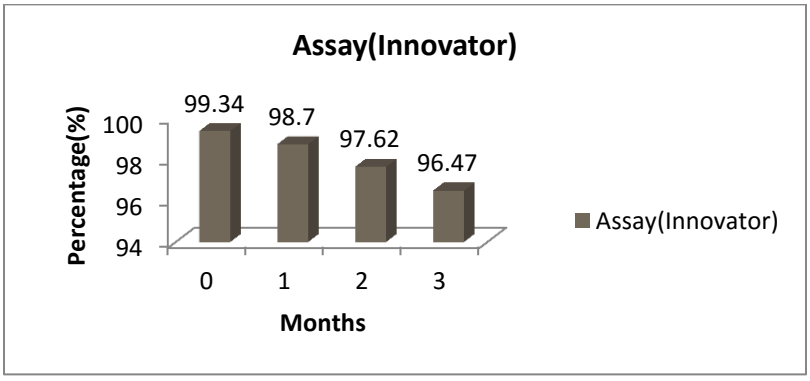


Figure No.10: Assay – Innovator, stability batch



Inference:

The drug assay profile were came within the limits, at the end of 3rd month of 40˚C ± 2˚C / 75% RH ± 5% RH . From this stability studies, it is concluded that the formulated tablets are stable.

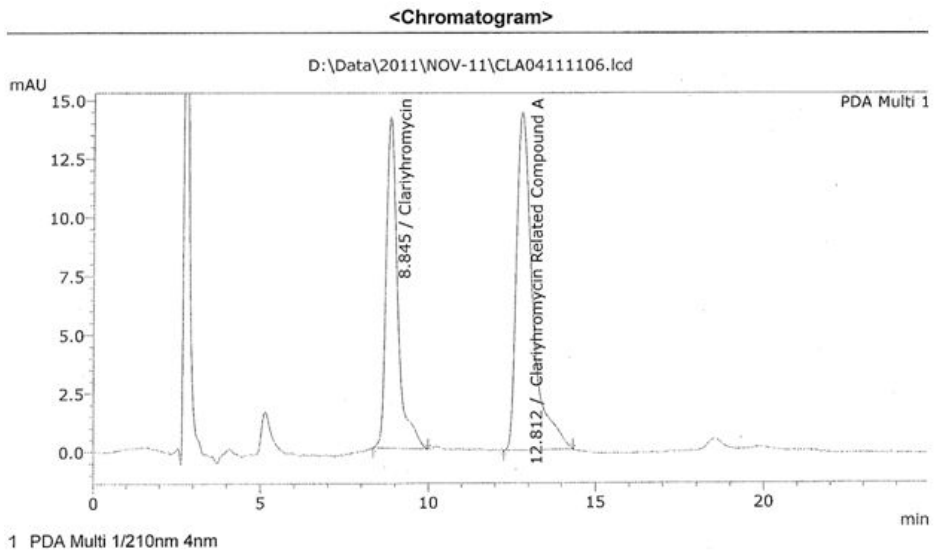
5.9. CHROMATOGRAM OF CLARITHROMYCIN TABLETS

1. Chromatogram of clarithromycin and their related substance

Table No. 38: Chromatogram of clarithromycin and their related substance

S.No.	Name	Retention time(min)	Area(AU)	Area(%)	Tailing factor
1	Clarithromycin standard	8.845	338781	40.81	1.99
2	Clarithromycin related compound A	12.812	491391	59.19	2.13

Figure No. 11: Chromatogram of clarithromycin and their related substance



2. Clarithromycin (OF7) stability batch chromatograms (dissolution profile)

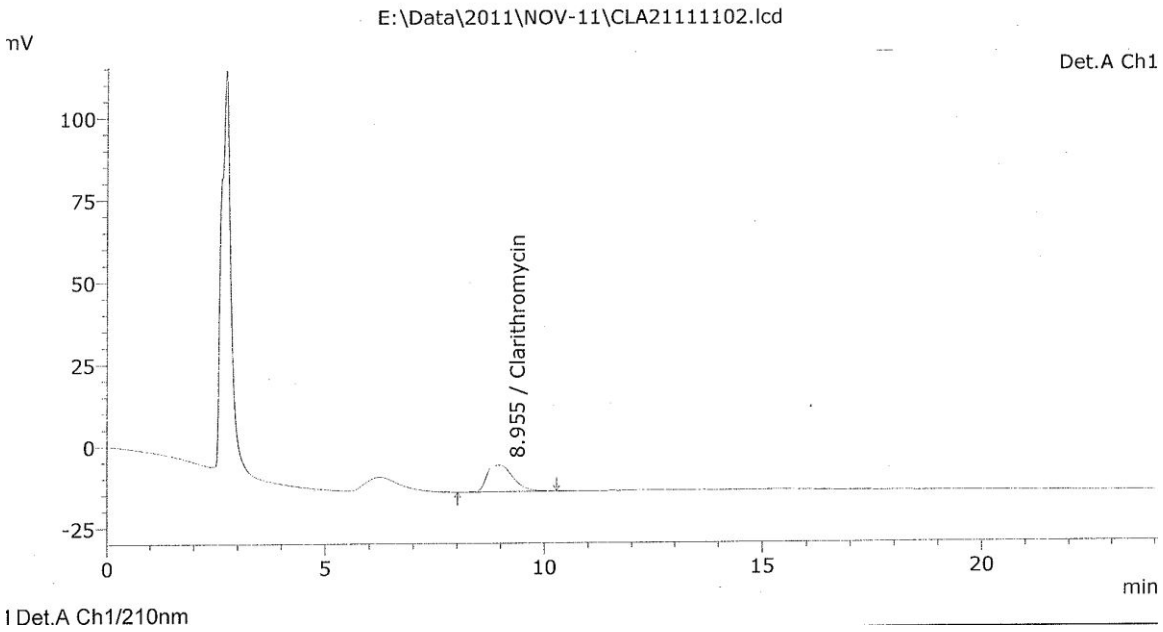
Table No. 39: Clarithromycin stability batch chromatograms (dissolution profile)

S.No.	Name of the sample	Retention time (min)	Area (AU)	Area (%)	Tailing factor

1	Standard	8.955	338875	100.00	1.306
2	OF7 initial	8.953	306763	100.00	1.39
3	OF7 1st month	8.956	304985	100.00	1.38
4	OF72nd month	8.951	304521	100.00	1.34
5	OF7 3rd month	8.950	301055	100.00	1.30

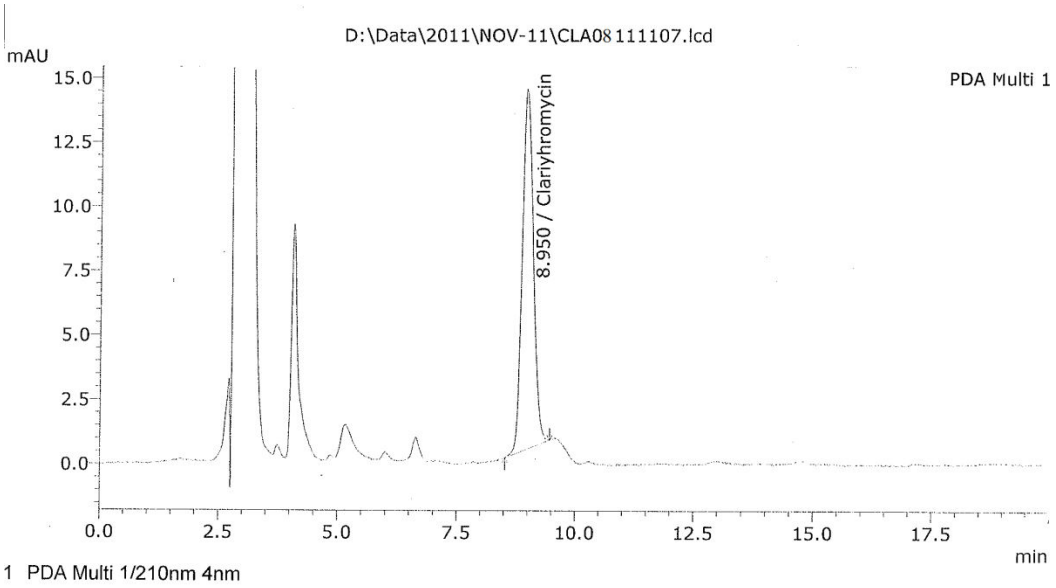
a) Chromatogram of clarithromycin standard (Standard)

Figure No. 12: Chromatogram of clarithromycin standard (Standard)



b) Chromatogram of clarithromycin tablets (40°C ±2%,75%±5% RH)-3rd month

Figure No. 13: Chromatogram of clarithromycin tablets



3. Clarithromycin (OF7) stability batch chromatograms (Assay)

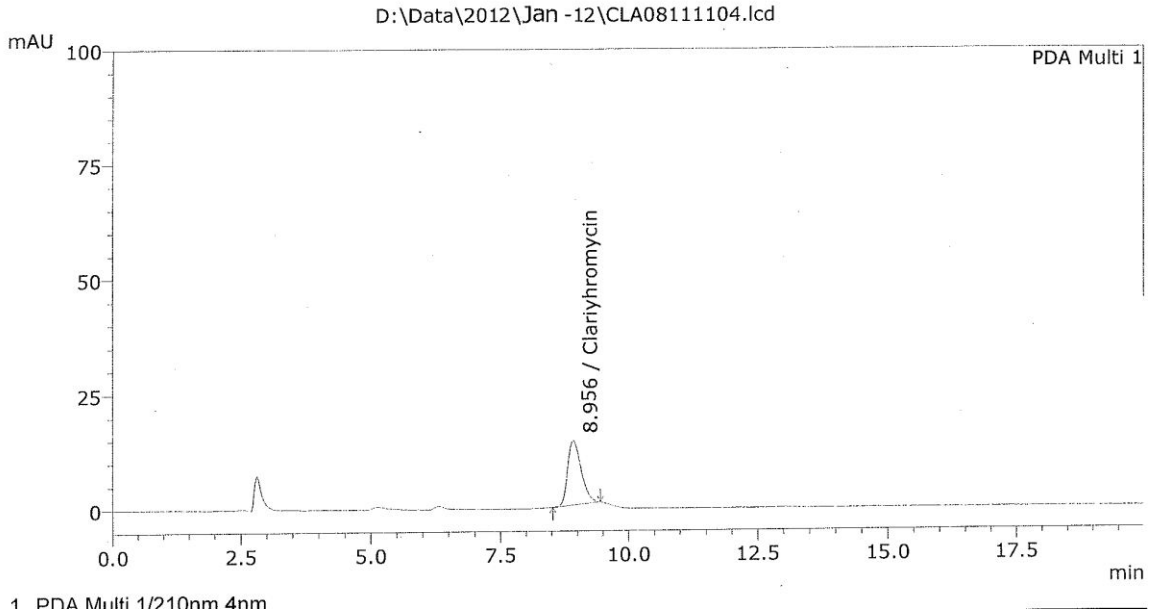
Table No. 40: Clarithromycin stability batch chromatograms (Assay)

S.No.	Name of the sample	Retention	Area(AU)	Area (%)	Tailing

		time (min)			factor
1	Standard	8.956	338875	100.00	1.38
2	OF7 initial	8.957	346898	100.00	1.35
3	OF7 1st month	8.958	341938	100.00	1.35
4	OF72nd month	8.952	337231	100.00	1.34
5	OF7 3rd month	8.954	328283	100.00	1.38

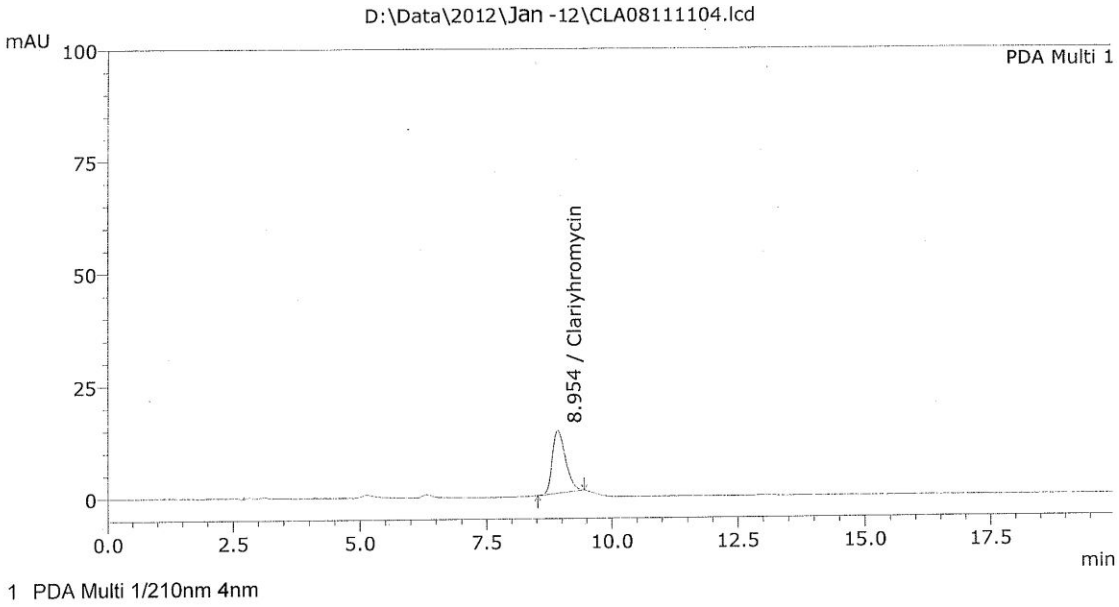
a) Assay of clarithromycin (standard)-(40°C ±2%, 75%±5% RH)-3rd month

Figure No. 14: Chromatogram of assay for clarithromycin (Standard)



b) Assay of clarithromycin tablet (40°C ±2%, 75%±5% RH)-3rd month

Figure No. 15: Chromatogram of assay of clarithromycin tablets



SUMMARY

The present study of clarithromycin film coated tablets were developed with a view to deliver the drug immediately. The film coated immediate release tablets were evaluated and the details of results and discussion were given in the following sections.

Drug Excipient-Compatibility Study:

The FT-IR spectrum of clarithromycin raw material was shown in Fig.No. 4. The spectrum of Clarithromycin raw material shows the presence of peaks at 3470 cm-1, 2976 cm-1 1729 cm-1 , 1458 cm-1 ,1266 cm-1, 1096 cm-1 and 1052 cm-1 of OH, CH, C=O, CH3, CH2, C-N, C—O stretching respectively.

The FT-IR spectrum of the combined clarithromycin and excipients was shown in the Fig.No 5. The spectrum shows the presence of peaks at 3465 cm-1 , 2975 cm-1, 1730 cm-1 , 1459 cm-1 ,1228 cm-1 ,1026 cm-1 and 1011 cm-1of OH, CH, C=O, CH3, CH2, C-N, C—O stretching respectively, indicating there is no interation between the drug and the excipients.

Observation of clarithromycin tablet formulation during inprocess:

Initial batches, that is F1 to F3 were formulated with wet granulation by aqueous method with hydroxy propyl cellulose (2.35%) as a binder, MCC PH 101 is used as a diluent. These formulations shown a sticking problem during inprocess compression, which may be due to high moisture content and low amount of lubricants.

Therefore, the next trial (F4) were again formulated with non-aqueous granulation with povidone (4.029%) and lubricants like aerosil (0.529%), magnesium stearate (1.0%), talc (0.5%). In this trial, sticking was not observed. But roughness is observed during compression.

In the trial F5, in this formulation, MCC PH 101 is replaced by MCC PH 102 (4.23%) and colloidal silicon dioxide (0.7%) in the granulation. In addition, lubricants are

increased to avoid the sticking problem during compression. Here, all the parameters were found satisfactory.

In the F6 trial, some amounts of lubricants are increased in both upper and lower granulation parts. All the parameters were found to be satisfactory and this batch tablets were kept for stability studies. During stability studies, dissolution was failed in the 1st month for 40oC ± 2oC/75% ± 5%. Because, while dissolution, the tablet breaks into 2-3 parts and not disintegrated uniformly. The percentage drug release was also less compared to initial month of stability studies. This problem may be due to insufficient disintegrates in the formulation.

In the trial F7, this procedure is also same as trial F5. However, in this formulation, the concentration of MCC PH102 is decreased and pre-gelatinized starch was included in the lubrication part of the formulation for better disintegration during the dissolution. In this, all the parameters were found satisfactory during pre-compression and post-compression. During dissolution of 1st month of stability studies, all the tablets were not disintegrated evenly and divided in to 2 to 3 parts. This may be due to presence of aerosil in the upper granulation part.

In the trial F8, in this formulation, colloidal silicon dioxide was replaced from granulation part to the lubrication part. In addition, increase the lubricants concentration to avoid sticking. In this trial, all the parameters were found satisfactory at initial stages.

Therefore, to know the best formula, formulation F8 undergoes the 32 randomized full factorial optimization studies. Based on preformulation studies, the amounts of croscarmellose sodium (X1) and microcrystalline cellulose PH102 (X2) were selected as the independent factors, studied at 3 levels each (-1, 0, +1). The percentage drug release (y1) and disintegration time (y2) were taken as dependent factors.

Optimized batches were coded as OF1, OF2 OF3, OF4, OF5, OF6, OF7, OF8 and OF9. The Precompression and post compression studies was performed for all the optimized batches. Results were found to be similar for all the optimized batches and innovator product. From these studies, OF7 was selected and compared all the evaluation profiles with the innovator product during the period of stability studies.

EVALUATION OF BLEND MATERIALS OF CLARITHROMYCIN TABLETS:

The angle of repose of formulation blends of clarithromycin F1 to F8 were in the range of 30.14±0.29° to 34.93±0.68°. The bulk density, tapped density, Carr's index, hausners ratio were found in the range of 0.472 to 0.534g/cc, 0.55 to 0.61g/cc, 10 – 15.33g/cc and 1.11-1.18 respectively. It reveals that all the formulation blends were having good flow characteristics and flow rates.

The results of granule evaluation were given in Table No. 26.

Tablet characteristics of clarithromycin uncoated IR tablets:

The tablets of different formulation were subjected to various evaluation tests such as thickness, hardness, friability and drug content. All the formulations of clarithromycin showed uniform thickness.

The hardness and percentage friability of all batches (F4 to F8) of clarithromycin ranged from 9.5 – 10.0 kg / cm2 and 0.1 – 0.3 % respectively. The disintegration of all batches (F4 to F8) of clarithromycin is found in limits 1.22-1.54.

The drug content of clarithromycin uncoated tablets was found to be uniform among all the formulations which ranges from 99.01% –104.67%. The evaluation results of clarithromycin uncoated IR tablet were given in Table No. 28

Tablet characteristics of clarithromycin coated IR tablet:

The tablets of different formulation were subjected to various evaluation tests such as thickness, disintegration and drug content. All the formulations of clarithromycin showed uniform thickness.

The disintegration time of all batches (F4 to F8) of clarithromycin is found within limits 2.24-2.27.

The drug content of clarithromycin coated tablets was found to be uniform among all the formulations, which ranges from 98.87% – 104.54%. The evaluation results of clarithromycin IR tablet were given in Table No. 29.

Tablet characteristics of clarithromycin optimized coated IR tablet:

The tablets of different formulation were subjected to various evaluation tests such as thickness, disintegration and drug content.

The disintegration of all batches (OF1 to OF9) of clarithromycin are found within limits 2.08-3.06 min

The drug content of clarithromycin coated tablets was found to be uniform among all the formulations which ranges from 99.99% – 104.54%. The evaluation results of clarithromycin IR tablet were given in Table No. 30.

In-vitro drug release study from F4 to F8

The in vitro drug release of all the formulations of clarithromycin from F4 to F8 at 5th, 10th, 15th, 20th and 30th minutes was found to be in the range of 68.55-69.19%, 81.57-85.31%, 91.23-96.27%, 92.67-98.36%, and 96.34-101.15% respectively. Among all the formulations, F8 were found to be the best (F8-Clarithromycin-500mg, CCS-17 mg, povidone - 35mg, CCS (L) - 25.50mg, MCC102-196mg, pregelatinized starch (L)-50mg, talc - 9.50 mg, aerosil l-9.50 %, magnesium stereate-7.50mg) since its release was satisfactory i.e., 69.19%,85.31%, 96.27%,98.36%, 101.15% at 5th,10th,15th,20th,30th minute.

Comparison of clarithromycin IR tablets (OF7) with innovator product

Table No: 33 gives the comparison of in-vitro dissolution profile of clarithromycin IR batch (OF7) with the innovator product. The drug release of clarithromycin IR tablet was found to be 70.83%, 84.96%, 95.45%, 98.46%, and 101.62% at 5th, 10th, 15th, 20th, 30th min respectively.

The drug release of innovator product was found to be 80.88%, 95.46%,97.55%,99.34% and 102.56% at 5th,10th,15th,20th ,30th minute respectively for clarithromycin .

In Table No:33, the formulation OF7 shows the dissimilarity factor f1 and similarity factor f2 values are within the specified limits (i.e., 5.147 and 59.658) when compared with the innovator product. Hence, formulation OF7 was selected for stability studies.

Stability Studies

The clarithromycin immediate release tablets (OF7) was kept on stability at 40° C/ 75 % RH and the three month accelerated condition results were found to be satisfactory. The stability study data's were depicted in the Table No.35-37.

CONCLUSION

The objective of the present study was to formulate, optimize and evaluate clarithromycin immediate release film coated tablet.

Literatures regarding, clarithromycin tablet dosage form preparation, excipients selection, manufacturing method, etc., has been collected and reviewed.

In this work, selection of excipient was done based on standard innovator product cited from pack insert. Excipients include croscarmellose sodium, povidone, pregelatinized starch, microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate. Quantities of the excipients were selected by performing finger print method, which is an IHS of Fourrts India Laboratory.

Preformulation studies have also been performed to study the nature of API and compatibility of API with excipients by physical observation and FT-IR studies. The results show that API was compatible with all the excipients selected.

The tablets were formulated by wet granulation method using the selected excipient quantities. The formulated tablets were tested for both pre-compression parameters and post compression parameters as per requirements of standards.

Pre-compression parameters such as bulk density, tapped density, compressibility index, Hausner's ratio and angle of repose were performed and found to show excellent flow properties.

Post compression parameters such as weight variation, hardness, thickness, friability, disintegration, drug content and percentage drug release were performed and found to be within the limits.

The formulated trial batch was taken for optimization by full factorial design. i.e., croscarmellose sodium (X1) and microcrystalline cellulose sodium (X2) as 2 independent variables at 3 levels -1, 0 and +1.

Optimized batches were coded as OF1, OF2, OF3, OF4, OF5, OF6, OF7, OF8 and OF9. The in vitro dissolution study was performed for all the optimized formulations. Similarity is found in the results of all the optimized formulations and innovator product. Among the entire optimized batches, formulation OF7 has been selected for calculating similarity factor, since it shows better results (i.e., faster disintegration time and rapid drug release) than other optimized batches. Similarity factor was calculated by comparing the in-vitro drug release profile for batch OF7 with the innovator product. The dissimilarity factor f1 value of 5.147 and similarity factor f2 value of 59.658 indicates that the two products were similar in in-vitro drug release.

The tablets of OF7 optimized batch was subjected to accelerated stability studies as per ICH guidelines. The results of stability studies showed that there were no significant changes in the physical and chemical parameters studied.

From this study, it was concluded that optimized clarithromycin tablet (OF7) containing croscarmellose sodium (3.029%) and pregelatinized starch (6.029%) could be manufactured with reproducible characteristics from batch to batch.

FUTURE STUDY

The finding of the present study has initiated the company to go in for scale up trial. Based on the reproducible results produced from batch to batch the company will decide to launch the product in the future.

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